EXTENDED REPORT

Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth?

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ABSTRACT

Objectives To explore criteria regulating treatment with reimbursed biologic disease-modifying antirheumatic drugs (bDMARDs) in patients with rheumatoid arthritis (RA) across Europe and to relate criteria to indicators of national socioeconomic welfare.

Methods A cross-sectional study among 46 European countries. One expert from each country completed a questionnaire on criteria regulating the start, maintenance/stop and switch of reimbursed bDMARDs. A composite score was developed to evaluate the level of restrictions in prescription of a first bDMARD (0=highly restricted, 5=most liberal). The level of restrictiveness was correlated with national socioeconomic welfare indicators.

Results In 10 countries (22%), no bDMARD was reimbursed. Among 36 countries with at least one biologic reimbursed, 23(64%) had no requirement for disease duration to initiate a biologic. Half of the countries required a failure of two synthetic DMARDs to qualify for therapy. 31 countries specified a minimum level of disease activity to be fulfilled and in 20 (56%) countries cut-off for disease activity score with 28-joint assessment was higher than 3.2. Four countries (11%) had the maximum composite score (most liberal) and 20 (56%) scored between 0 and 2 (more restrictive). Criteria for initiation of a bDMARD were negatively associated with countries' socioeconomic welfare (−0.34 to −0.64), and a moderate positive correlation was found between the composite score and welfare indicators (0.59–0.72). Only some countries had regulations for stopping (n=14(39%)) or switching (n=19(53%)).

Conclusions Clinical criteria regulating prescription of bDMARDs in RA differ significantly across Europe. Countries with lower socioeconomic welfare tend to have stricter eligibility criteria, pointing to inequities in access to treatment.

INTRODUCTION

In the treatment of patients with rheumatoid arthritis (RA), the availability of biologic disease-modifying antirheumatic drugs (bDMARDs) improved the ability to control disease activity, decreased the need for surgery and increased work participation and quality of life.[1 2] However, bDMARDs are costly, and partly for this reason reimbursement criteria and/or clinical recommendations/guidelines have been formulated across countries to regulate access to these treatments.[3]

We previously reported that access to conventional treatment as well as biological treatment across each dimension of access (availability, affordability and acceptability) was more limited in countries with lower socioeconomic welfare.[4 5] Access to therapy was operationalised through system characteristics (eg, price of bDMARDs, date of reimbursement), while clinical criteria regulating therapy were not covered.[4] Discrepancies in these criteria can contribute to inequalities in access and consequently uptake of medications and health outcomes. In 2009, Emery *et al* reviewed the clinical guidelines for eligibility of patients with RA for treatment with biologics in 10 European countries and confirmed large variations across countries, particularly in terms of disease duration and disease activity level required for initiation of anti-tumour necrosis factor-α therapy.[6] This review included clinical guidelines published before 2007 and was limited to a relatively small number of countries from the European Union. Nowadays, more biologics are available for the treatment of RA, making it important to also gain insight into criteria to stop and switch between bDMARDs, and to explore the possible existence of a maximum number of bDMARDs that can be prescribed to one patient. Moreover, no attempt has until now been made to link variation in regulations to start a bDMARD and the level of socioeconomic welfare of the country and the uptake of bDMARDs or RA-related health status in that country.

The objective of the present study was therefore to review the criteria regulating treatment with bDMARDs (including start and maintenance) in patients with RA across the entire European Region, relate them to indicators of national socioeconomic welfare and shed light on potential impact of these criteria on uptake of treatments and health outcomes.

METHODS

Data collection

All countries of the European Region were invited to participate, with the exception of small

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(city)-states and Israel, which were excluded from the start, and Kyrgyzstan, where it turned out to be impossible to establish collaboration.[4]

Data on the eligibility for initiation and maintenance/stop or switches between bDMARDs in patients with RA were collected, as of May 2011, by a rheumatologist or an expert from each country. Answers were carefully checked and collaborators were contacted to confirm the results.

First, experts were asked whether at least one bDMARD was reimbursed. For those countries confirming an official reimbursement, medical specialties authorised to prescribe biologics to patients with RA were identified, as well as whether either reimbursement criteria or clinical recommendations (or both) were predominantly regulating prescription. Further, information was collected on the following requirements before starting a bDMARD (if applicable): (a) minimal disease duration; (b) failure of synthetic DMARDs (sDMARDs), including type, number and length of treatment; and (c) clinical criteria, such as level of disease activity where applicable (eg, disease activity score with 28-joint assessment—DAS28[7]). Finally, questions were asked on (a) time point to assess response; (b) requirements to alter the frequency and/or dose of a biologic; (c) criteria to stop (or maintain, as reported) therapy with biologics; (d) criteria to switch between agents; (e) existence and (if applicable) frequency of official controls on the adherence to the reimbursement criteria; and (f) maximum number of biologics that could be tried on one patient.

Data on indicators of socioeconomic welfare and health status of RA patients

Data on the number of inhabitants and indicators of socioeconomic welfare (gross domestic product (GDP), total health expenditure and median income) were collected for each country. Values were retrieved from web-based sources (latest available data for 2008–2011) and adjusted to purchasing power parities (2010, expressed in international dollars, int.$).[8–10]

Data on RA health status and uptake of bDMARD (percentage of patients ever treated with a biologic) were available for 21 countries from the Quantitative Standard Monitoring of Patients with RA (QUEST RA) study, a multinational cross-sectional study of non-selected outpatients with RA on disease outcome. This provided clinical information: DAS28; swollen joint count; tender joint count; Health Assessment Questionnaire[11]; Physician (MD) and Patient (PT) Global Visual Analogue Scales and erythrocyte sedimentation rate.[5 12]

Computed variables and composite score for clinical eligibility criteria

The individual criteria to assess eligibility for a first biologic (disease duration, disease activity level and number of sDMARDs to be failed) were inspected and categorised into two or three broad groups so that the most frequent patterns could be identified (tables 1 and 2). In order to compute this composite score, requirement for a specific disease duration was categorised as 'any requirement' (0 point) or 'no requirement' (1 point); the number of sDMARDs to be failed as 'more than two' (0 point), 'two' (1 point) and 'less than two'(2 points) and the level of disease activity (based on the level of DAS28 since this appeared to be the criterion applied by most regulations) as 'DAS28 cut-off >3.2 or its equivalent' (0 point), 'DAS28 cut-off ≤3.2 or its equivalent' (1 point) and 'no requirement' (2 points). In addition, a composite score was computed for each country, which was the simple sum of the scores on the individual criteria and varied between 0 and 5; the higher the score, the easier the access. Criteria for stop/maintenance (at 6 months), switch and change of frequency/dose were also categorised after inspection into broad groups to reflect the patterns (table 3).

Statistical analysis

Data were analysed for all countries using descriptive statistics. Score on the individual criteria (original values) and composite index were compared between the 27 EU and the 9 non-EU countries by means of Mann–Whitney U test (skewed distribution).

The association between the sources of prevailing regulation (only reimbursement criteria, only clinical recommendations or both) and the frequency of controls on prescriptions from the regulating agencies was investigated through χ^2 test.

Correlations (Spearman) were first established between the individual criteria for initiation of a first bDMARD and, next, between the crude individual criteria and the composite score with (a) indicators of socioeconomic welfare; (b) uptake of bDMARDs; and (c) indicators of RA health status. Analysis was done for all countries and EU countries separately. Coefficients >0.5 but ≤0.80 were assumed to be moderate and >0.8 strong.[13] SPSS V.19.0 was used.

RESULTS

In total, 46 countries (response rate 94%) provided data. An overview of the clinical criteria for eligibility and maintenance of biologic in each of the countries is presented in table 1. In 10 countries (22%), no bDMARD was reimbursed. Among the remaining 36, Luxemburg had no regulation for the start of a reimbursed bDMARD, in 11 (31%) reimbursement criteria were the major source of eligibility criteria, while in 7 (19%) clinical recommendations predominated and in 16 (44%) both reimbursement criteria and clinical recommendations were used (usually because they were similar or clinical criteria complemented reimbursement criteria) for decisions to start a biologic (table 1). Albania had no written source of regulation but reported the criteria used in practice. Countries differed with respect to frequency of controls of the adherence to formal recommendations. Thirteen countries (36%) reported controls were 'frequent' or 'always', in 17 countries (47%) controls were 'rare' or 'sometimes' and respondents from six countries (17%) reported no controls of adherence to existing criteria. No association between the type of prevailing regulation (ie, reimbursement criteria, clinical recommendations or both) and reported frequency of controls was detected (p=0.43).

In 24 countries (67%), only rheumatologists had permission to prescribe bDMARDs to patients with RA, while in the rest other specialties such as Dermatology (22%), Gastroenterology (22%), Internal medicine (25%), General practice (11%) and other (14%) were similarly entitled to prescribe (table 1).

Among 36 countries with at least one biologic reimbursed, 23 (64%) had no requirement on disease duration to initiate a bDMARD, while for the remaining countries the prespecified minimum duration ranged from 3 to 12 months. With respect to the number of sDMARDs to be failed, the most common criterion (n=18(50%)) was the failure of two DMARDs. A minimum level of disease activity or severity was mandatory in 31 (86%) countries but was not specified in Germany, Ireland, Luxemburg, Malta and Switzerland. In 11 countries (31%), patients with a DAS28 of 3.2 qualified to obtain access to bDMARDs, but in 20 countries (ie, over 50%) this requirement was stricter than a DAS28 of 3.2 (or equivalent), meaning that the cut-off to start a biologic was higher than 3.2 (tables 1 and 2).

Table 1 Clinical criteria for eligibility and maintenance of treatment with bDMARDs in 36 European countries with at least one biologic reimbursed

Country	Major source of eligibility criteria	Who can prescribe bDMARDs to patients with RA	Requirement to start the first biologic: Minimum disease duration	Requirement to start the first biologic: Level of disease activity	Requirement to start the first biologic: Number of sDMARDs to be failed, type of DMARD and length	Time point for the first assessment of response (weeks)	Criteria to stop at 6 months*	Criteria to switch at 6 months*	Composite score for restrictiveness of clinical criteria (0–5)
Albania (no written source provided, criteria reported are those used in practice according to contact person)	REIM	Rheumatology	No requirement	DAS28>4.5	2 sDMARDs: MTX (20 mg/week) and SSZ (2.5 g/day)	NA	No criteria	No criteria	2
Austria[24–26]	REIM=GUID	Rheumatology	No requirement	Moderate to high disease activity	1 sDMARD: MTX in adequate dose and adequate duration	12	No criteria	Moderate disease activity	4
Belgium[27]	REIM	Rheumatology	No requirement	DAS28>3.7	2 sDMARDs: MTX (15 mg/week)+another DMARD	24	DAS28>5.1 and improvement in DAS28 <1.2 OR DAS28 <5.1 and improvement in DAS28 <0.6	No criteria	2
Bulgaria[28]	REIM	Rheumatology	6 months	DAS28>5.1	2 sDMARDs: MTX (20 mg/week) and LEFL (20 mg/day) for 6 months	12	No criteria	No criteria	1
Croatia[29–31]	REIM=GUID	Rheumatology	6 months	DAS28>5.1 AND HAQ 1.0–2.5 AND TJC>6 AND SJC>6 AND ESR>28 AND CRP>12 AND ACR I–III	2 sDMARDs: MTX (20 mg/week)+another DMARD for 6 months	12	(DAS28>3.2 and improvement in DAS28 <1.2) OR improvement lower than ACR20	No criteria	1
Cyprus[32]	REIM=GUID	Rheumatology +Dermatology +Gastroenterology +Internal medicine	6 months	DAS28>4	2 sDMARDs: MTX +another DMARD for at least 6 months	12–16	DAS28>3.2 and improvement in DAS28<1.2	DAS28>3.2 and improvement <1.2	1
Czech Republic[33 34]	REIM=GUID	Rheumatology	6 months	DAS28>3.9	1 sDMARD:, MTX (20 mg/week) OR LEFL (20 mg/day) OR SSZ (2 g/day) for 3–6 months	12–16	No criteria	Moderate disease activity	2
Denmark[35]	GUID	Rheumatology	No requirement	DAS28>3.2 OR radiographic progression	2 sDMARDs: MTX (25 mg/week) and SSF (2 g/day)	12–16	No criteria	No criteria	3
Estonia[36 37]	REIM+GUID	Rheumatology	6 months	DAS28>4.6 AND TJC>8 AND SJC>6 AND morning stiffness>1 h AND ESR 30 AND CRP 25 mg/L AND active visceral disease by expert opinion	4 sDMARDs: including MTX (25 mg/week) and Prednisone (7.5 mg/week)	12–24	Improvement in DAS28<1.2	DAS28>4.6 AND TJC>8 AND SJC>6 AND morning stiffness>1 h AND ESR 30 AND CRP 25 mg/L AND active visceral disease by expert opinion	0

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Table 1 Continued

Country	Major source of eligibility criteria	Who can prescribe bDMARDs to patients with RA	Requirement to start the first biologic			Time point for the first assessment of response (weeks)	Criteria to stop at 6 months*	Criteria to switch at 6 months*	Composite score for restrictiveness of clinical criteria (0–5)
			Minimum disease duration	Level of disease activity	Number of sDMARDs to be failed, type of DMARD and length				
Finland[38]	REIM	Rheumatology +Internal medicine	No requirement	Active disease	3 sDMARDs	NA	No criteria	No criteria	2
France[39]	GUID	Rheumatology +Internal medicine	No requirement	DAS28>5.1 OR lower if corticodependence or structural damage progression	None to 1 sDMARD: for the majority of biologics, only MTX is mentioned without any strict dose or regimen	12	No criteria	No criteria	3
Germany[40]	REIM+GUID	Rheumatology +Dermatology +Gastroenterology +Internal medicine +GP+other specialties	No requirement (min. 3 months recommended)	No requirement	No requirement (2 sDMARDs: including MTX, LEF, SSZ, HCQ, Gold and CyA recommended)	12	No criteria	No criteria	5
Greece[40a]	REIM+GUID	Rheumatology	No requirement	DAS28>5.1 or DAS28>3.2 AND presence of adverse prognostic factors * (≥2/5) *Adverse prognostic factors: RF/anti-CCP, joint erosions in X-ray, HAQ>1, large joint involvement and extra-articular disease	1. In established RA: 2 sDMARD either MTX (≥15 mg/week) or LEFL (20 mg/day) or 1 sDMARD if adverse prognostic factors* (≥2/5) 2. In early RA anti-TNF agents are allowed (combined to MTX) as the first therapy in case of highly active disease (DAS28>5.1) AND presence of adverse prognostic factors* (>2/5)	12	DAS28>3.2	DAS28>3.2	2
Hungary[42 43]	REIM+GUID	Rheumatology	3 months	DAS28>5.1	2 sDMARDs: MTX and another sDMARD in 'full dose or tolerable dose'	12	Improvement DAS28 <1.2	Improvement in DAS28 <1.2	1
Iceland[41]	REIM+GUID	Rheumatology +Dermatology +Gastroenterology	No requirement	DAS28 3.2 (progressing radiographic damage facilitates initiation of biologics)	1 sDMARD: MTX (20 mg/week)	24	No criteria	DAS28>3.2	4
Ireland[44]	GUID	Rheumatology +Dermatology +Gastroenterology +Internal medicine +other specialties	No requirement	No requirement	1 sDMARD: MTX (25 mg/week) for 3 months	12	No criteria	No criteria	5
Italy[45]	GUID	Rheumatology +Dermatology +Gastroenterology	3 months	DAS28>3.2	1 sDMARD: MTX (15 mg/week) for 3 months	NA	No criteria	No criteria	3
Latvia[46]	REIM	Rheumatology	No requirement	DAS28>3.2	3 sDMARDs: MTX (20 mg/week)+another 2 DMARDs for 3–6 months	12	No criteria	DAS28>3.2	2

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Table 1 Continued

Country	Major source of eligibility criteria	Who can prescribe bDMARDs to patients with RA	Requirement to start the first biologic: Minimum disease duration	Requirement to start the first biologic: Level of disease activity	Requirement to start the first biologic: Number of sDMARDs to be failed, type of DMARD and length	Time point for the first assessment of response (weeks)	Criteria to stop at 6 months*	Criteria to switch at 6 months*	Composite score for restrictiveness of clinical criteria (0–5)
Lithuania[47–49]	REIM=GUID	Rheumatology	No requirement	DAS28>5.1	2 sDMARDs: choice MTX (25 mg/week) for 3 months, AZATH (100 mg/day) for 3 months, LEFL (20 mg/day) for 3 months, HCQ (400 mg/day) for 3 months and SSZ (2 g/day) for 6 months	12	Improvement in DAS28 <1.2 after 3 months	Improvement in DAS28 <1.2 after 3 months	2
Luxemburg	No regulation in access to reimbursed biologics	Rheumatology +Dermatology +Gastroenterology +Internal medicine +GP+other specialties	No requirement	No requirement	No requirement	NA	No criteria	No criteria	5
Macedonia[50]	REIM	Rheumatology	No requirement	DAS28>4.2 AND SJC>=6	2 sDMARDs for 6 months	6–12	No criteria	No criteria	2
Malta[51]	REIM	Rheumatology	6 months	No requirement	2 sDMARDs: choice MTX for 6 months (at least 2 months on 15 mg/week), LEFL (20 mg/day) for months and SSZ (2 g/day)	12	DAS28>3.2 and improvement in DAS28 <1.2	No criteria	3
Montenegro[52]	REIM	Rheumatology	6 months	DAS≥5.1 AND HAQ between 1 and 2.5 AND ACR I–III AND increased ESR and CRP AND SJC≥6 AND Painful joints ≥6	2 sDMARDs: choice MTX (20 mg/week), SSZ (2 g/day) and LEFL(20 mg/day) for 3 months each	NA	No criteria	Improvement in DAS28 <1.2	1
The Netherlands[53]	REIM+GUID	Rheumatology	No requirement	DAS28>3.2	2 sDMARDs: MTX and another sDMARD	NA	Improvement in DAS28 <1.2	Improvement in DAS28 <1.2	3
Norway[54]	REIM=GUID	Rheumatology	No requirement	DAS28≥3.2	1 sDMARD	12–24	No criteria	No criteria	4
Poland[55]	REIM	Rheumatology	12 months	DAS28>5.1 OR DAS>3.7 if joints of lower limbs are involved	2 sDMARDs: MTX (25 mg/week) for at least 3 months+another DMARD	9	Improvement in DAS28<1.2 in 90 days	Improvement in DAS28 <1.2 in 90 days	1
Portugal[56]	REIM+GUID	Rheumatology +Internal medicine	No requirement	DAS>3.2 OR 2.6<DAS <3.2 AND (worsening of HAQ>0.22 (6/6M) OR worsening of X-ray scores: Larsen>6/SvdH>5 (12/12M))	1 sDMARD: MTX in conventional dose for 3 months or another DMARD for 6 months	12	Improvement in DAS28<1.2 OR Improvement in DAS28<0.6 in 3 months	Improvement in DAS28<1.2 OR <0.6 in 3 months	4
Romania[57]	REIM+GUID	Rheumatology	No requirement	DAS28>5.1, including minimum five joints with active synovitis AND at least two of the following: morning stiffness>60 min AND ESR 1 h>28 OR CRP>20 mg/mL	2 sDMARDs: choice MTX (20 mg/week), SSZ (3 g/day) and LEFL (20 mg/day) for 12 weeks each	24	No criteria	DAS28 is stable≥5.1 or improvement in DAS28 <1.2 between two separate evaluations	2

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Table 1 Continued

Country	Major source of eligibility criteria	Who can prescribe bDMARDs to patients with RA	Requirement to start the first biologic			Time point for the first assessment of response (weeks)	Criteria to stop at 6 months*	Criteria to switch at 6 months*	Composite score for restrictiveness of clinical criteria (0–5)
			Minimum disease duration	Level of disease activity	Number of sDMARDs to be failed, type of DMARD and length				
Serbia[58 59]	REIM+GUID	Rheumatology	6 months	Immediate and high activity (ACR I–III/DAS28>5.1 AND HAQ 1–2.5), high evolution	2 sDMARDs: MTX (7.5 mg/week) for at least 6 months AND choice: PRED (7.5 mg/day) at least 1 month or SSZ (500 mg/day) at least 1 month	12–16	No criteria	Improvement in DAS28 <1.2	1
Slovakia[60]	GUID	Rheumatology	6 months	Moderate to high disease activity	1 sDMARD: MTX (15 mg/week) for 3 months	12	No criteria	Moderate disease activity	3
Slovenia[61]	REIM=GUID	Rheumatology	No requirement	DAS28>4.2 AND SJC>=8	2 sDMARDs: MTX (20 mg/week) and choice LEFL (20 mg/day) or SSZ (2 g/day)	24	Improvement in DAS28<1.2	No criteria	2
Spain[62 62a]	GUID	Rheumatology	No requirement	DAS28≥3.2 OR SDAI≥11OR [(DAS28 between 2.6 - 3.2 OR SDAI 5-11) AND (persistent inflammation in joints considered important for the patient that does not resolve with local therapies or significant radiographic progression)]	1 sDMARD: MTX (25 mg/week)	12	No criteria	DAS28≥3.2 OR SDAI≥11OR [(DAS28 between 2.6 - 3.2 OR SDAI 5-11) AND (persistent inflammation in joints considered important for the patient that does not resolve with local therapies or significant radiographic progression)]	4
Sweden[63 64]	GUID	Rheumatology +Dermatology +Gastroenterology +Internal medicine +GP+other specialties	No requirement	DAS28>3.2 and several negative prognostic factors OR DAS28>5.1	No requirement	12	No criteria	DAS28>3.2 and several negative prognostic factors	3
Switzerland[65–67]	REIM	Rheumatology +Dermatology +Gastroenterology +Internal medicine +GP	No requirement	No requirement	1 sDMARD	NA	No criteria	No criteria	5
Turkey[68]	REIM	Rheumatology+other specialties	No requirement	DAS28>5.1	3 sDMARDs, including MTX	12	Improvement in DAS28 <1.2 OR improvement in DAS28 <0.6 in 3 months	No criteria	1
UK[69 70]	REIM	Rheumatology	6 months	DAS28>5.1	2 sDMARDs, including MTX	26	Improvement in DAS28<1.2	Improvement in DAS28 <1.2	1

*When criteria at different time points were defined, these are also added in the table with the corresponding information on the respective time point.
ACR, American College of Rheumatology; Anti-CCP, cyclic citrullinated peptide; AZATH, azathioprine; CRP, C reactive protein; Cya, cyclosporine; DAS28, disease activity score with 28-joint assessment; DMARD, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; GP, general practitioner; GUID, national guideline; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; LEFL, leflunomide; MTX, methotrexate; PRED, prednisolone; RA, rheumatoid arthritis; REIM, reimbursement criteria; RF, rheumatoid factor; SDAI, Simple Disease Activity Index; sDMARD, synthetic disease-modifying antirheumatic drugs; SJC, swollen joint count; SSZ, sulfasalazine; TJC, total joint count; TNF, tumour necrosis factor.

Table 2 Summary of clinical criteria for initiation of a first bDMARD for European countries with at least one biologic reimbursed (n=36)

Minimal clinical requirements for initiation of a bDMARD											
Disease duration				**DAS28 level**				**Number of sDMARDs to be failed**			
	N (%)	**Countries**	**Score***		**N (%)**	**Countries**	**Score***		**N (%)**	**Countries**	**Score***
No requirement	23 (64%)	AL, AT, BE, DK, FI, FR, DE,GR, IS, IE, LV, LT, LU, MK, NL, NO, PT, RO, SL, ES, SE, CH and TR	1	No requirement	5 (14%)	DE, IE, LU, MT and CH	2	<2	14 (39%)	AT, CZ, FR, DE, IS, IE, IT, LU, NO, PT, SK, ES, SE and CH	2
<6 months	12 (33%)	BG, HR, CY, CZ, EE, HU, IT, MT, ME, RS, SK and UK	0	Up to and including 3.2	11 (31%)	AT, DK, FI, IS, IT, LV, NL, NO, PT, SK and ES	1	2	18 (50%)	AL, BE, BG, HR, CY, DK, GR, HU, LT, MK, MT, ME, NL, PL, RO, RS, SL and UK	1
≥6 months	1 (3%)	PL	0	Above 3.2	20 (56%)	AL, BE, BG, HR, CY, CZ, EE, FR, GR, HU, LT, MK, ME, PL, RO, RS, SL, SE, TR and UK	0	>2	4 (11%)	EE, FI, LV and TR	0

*Score is the contribution to the composite score for restrictiveness of clinical criteria for initiation of a biologic disease-modifying antirheumatic drugs (bDMARD). DAS28, disease activity score with 28-joint assessment; DMARD, disease-modifying antirheumatic drug; sDMARDs, synthetic disease-modifying antirheumatic drugs.
AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxemburg; LV, Latvia; ME, Montenegro; MK, Macedonia; MT, Malta; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; SE, Sweden; SK, Slovakia; SL, Slovenia; TR, Turkey; UK, United Kingdom.

Table 3 Summary of clinical eligibility criteria for stop of the therapy, switch to another bDMARD or change frequency/dose of a biologic for European countries with at least one biologic reimbursed (n=36)

Stop due to inefficacy based on 6 -month assessment				Switch based on 6-month assessment				Change of frequency/dose		
Criteria*		**N (%)**	**Countries**	**Criteria***		**N (%)**	**Countries**	**Criteria**	**N (%)**	**Countries**
Not specified		22 (61%)	AL, AT, BG, CZ, DK, FI, FR, DE, IS, IE, IT, LV, LU, MK, ME, NO, RO, RS, SK, ES, SE and CH	Not specified		17 (47%)	AL, BE, BG, HR, DK, FI, FR, DE, IE, IT, LU, MK, MT, NO, SL, CH and TR	Not specified	18 (50%)	AL, AT, BE, BG, HR, EE, FI, FR, DE, LV, LU, ME, NL, PL, PT, SE, UK and MK
Yes, in terms of disease activity level 7 (19%)	DAS28≥3.2	5 (14%)	CY, MT, HR, HU and BE	Yes, in terms of disease activity level 11 (31%)	DAS28≥3.2 DAS28>4.6 †	6 (17%) 1 (3%)	CY, GR, IS, LV, ES and SE EE	Yes, frequency	15 (42%)	CY, CZ, DK, GR, IS, IE, IT, MT, NO, RO, RS, SL, ES, CH and TR
					DAS28>5.1 Moderate disease activity	1 (3%) 3 (8%)	RO AT, CZ and SK	Yes, dose	18 (50%)	CY, CZ, DK, GR, IS, IE, IT, LT, MT, NO, RO, RS, SK, SL, ES, CH, TR and HU
Yes, in terms of DAS28 improvement 14 (39%)	Δ <0.6	1 (3%)	BE	Yes, in terms of DAS28 improvement10 (28%)	Δ<0.6 in 3 months	1 (3%)	PT			
	Δ <1.2	14 (39%)	BE‡, HR, CY, EE, GR, HU, MT, NL, PT, SL, TR, UK, LT§ and PL§		Δ<1.2	10(28%)	CY, HU, LT§, ME, NL, PL§, PT, RO, RS and UK			

*Countries could have more than one criterion to stop/switch (disease activity level and/or disease activity improvement).
†Additional clinical criteria have to be satisfied besides the specified level of DAS28, for example, additional requirement for radiographic damage or specific levels of swollen joint count and/or total joint count.
‡If DAS28>5.1.
§After 3 months.
bDMARD, biologic disease-modifying antirheumatic drugs; DAS28, disease activity score with 28-joint assessment.
AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxemburg; LV, Latvia; ME, Montenegro; MK, Macedonia; MT, Malta; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; SE, Sweden; SK, Slovakia; SL, Slovenia; TR, Turkey; UK, United Kingdom.

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The timing for the first assessment of response was specified in 29 countries and varied from 9 to 24 weeks, with 16 countries defining this period as 12 weeks. Fourteen countries (39%) reported to have specific criteria to stop bDMARD before or at 6 months due to inefficacy (or for maintenance, from which stop criteria were extrapolated) (table 3). Of those, 11 (31%) required a minimum improvement in terms of disease activity (improvement of 1.2) before or at 6 months for therapy to be continued. Five of these countries (14%) required in addition a prespecified minimum level of disease activity to be achieved and this level corresponded to low disease activity (ie, DAS28 of 3.2) in four of them.

More than half of the countries (n=19, 53%) reported there were specific criteria for switching. These criteria included a minimum level of disease activity (n=11, 31%) and/or failure to reach a minimum improvement in disease activity (n=10, 28%). Half of the countries (n=18, 50%) had some regulation regarding the possibility to change the frequency and/or dose of a biologic (table 3). So far, no country introduced a maximum number of biologics that can be prescribed to one patient.

As for the composite score for clinical eligibility criteria that was based on the three criteria to initiate a bDMARD, 4 countries (11%) had the maximum (5) eligibility score (most liberal), 12 countries (33%) had score 3 or 4 and 20 (56%) scored between 0 and 2. Countries from Eastern Europe and Former Soviet Union were more likely to be classified in the more restricted scores (table 1, figure 1).

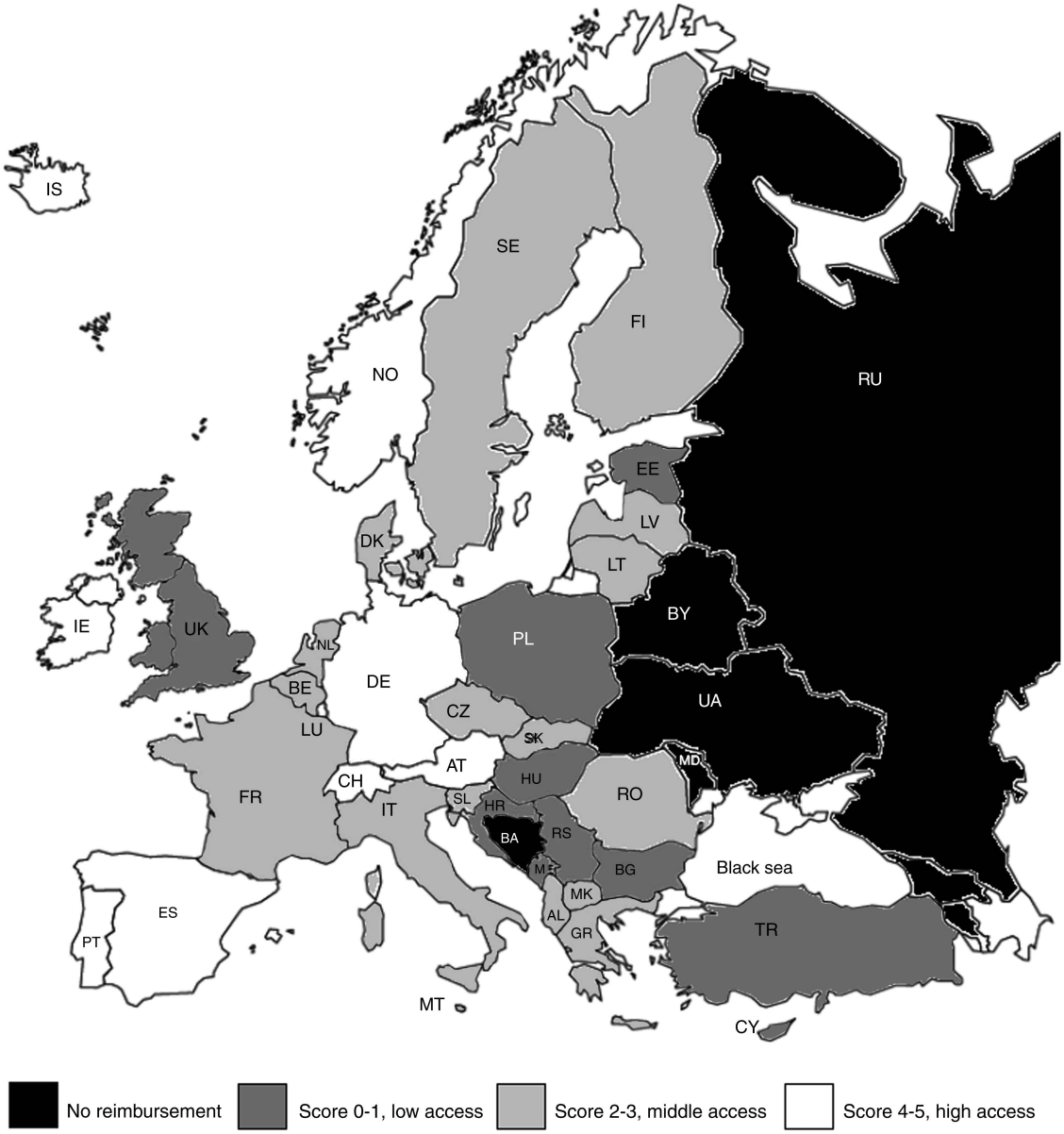

Figure 1 Composite score for restrictiveness of clinical criteria for initiation of a first reimbursed biologic (0–5) in the European Region (score is composed of (1) minimum required disease duration, (2) number of sDMARDs that have to be failed and (3) the level of DAS28). DAS28, disease activity score with 28-joint assessment; sDMARDs, synthetic disease-modifying antirheumatic drugs.
AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; HR, Croatia; CY, Cyprus; CZ, Czech Republic; EE, Estonia; FI, Finland; FR, France; DE, Germany; DK, Denmark; GR, Greece; HU, Hungary; IS, Iceland; IE, Ireland; IT, Italy; LV, Latvia; LT, Lithuania; LU, Luxemburg; MK, Macedonia; MT, Malta; ME, Montenegro; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; SK, Slovakia; SL, Slovenia; ES, Spain; SE, Sweden; CH, Switzerland; TR, Turkey; UK, United Kingdom.

The results for the eligibility for a first bDMARD did not differ significantly between the 27 EU and 9 non-EU members, neither for the individual criteria nor for the composite score (data not shown).

Correlation of clinical criteria and composite score for the eligibility for first biologic with GDP, uptake of bDMARDs and health status

The three individual clinical criteria to start a bDMARD were positively but weakly correlated with each other (Spearman coefficients 0.23–0.43), with the strongest association between the required level of disease activity and the number of sDMARDs to be failed (data not shown).

The level of DAS28 required before starting a bDMARD was moderately negatively associated with socioeconomic indicators (figure 2), weakly positively with the indicators of health status of RA patients and weakly negatively with the uptake of bDMARDs. The number of sDMARDs to be failed and requirement for minimum disease duration followed similar patterns (table 4).

The composite score was moderately positively associated with socioeconomic welfare and weakly to moderately negatively with the indicators of health status. Importantly, the composite score correlated moderately positively with the available data on the uptake of biologics. When analyses were limited to the 27 EU member states, correlations were weaker but the direction of the associations persisted (table 4).

DISCUSSION

This study highlights differences in clinical criteria that regulate initiation and continuation of treatment with reimbursed bDMARDs in patients with RA across the European Region. A first and foremost finding was that in 10 countries (all non-EU) no bDMARDs were reimbursed. In countries with bDMARDs reimbursed (n=36), criteria mainly regulated the start of the first biologic (all countries) in contrast with regulations for stopping/maintaining (n=14, 39%) or switching between drugs (n=19, 53%), which were not defined in every country. Limited regulations to stop bDMARDs are remarkable, because substantial costs can potentially be saved by stopping costly drugs that are (or have become) ineffective. On this line it is interesting to see that several new studies explore the impact of stopping bDMARDs in patients with sustained remission.[14]

Strikingly, in more than half of the countries (56%) the cut-off for the DAS28 as a criterion to start the first biologic was stricter than 3.2 (DAS28≥3.2). Furthermore, 13 countries (36%) required a minimum disease duration and 22 (61%) specified that more than one sDMARDs had to be failed before a bDMARD can be initiated.

Overall, the composite eligibility score indicated highly restricted access in one-third of the countries (scores 0 and 1). A strong negative association between the eligibility and GDP was found. Particularly non-EU countries had stricter eligibility criteria. In many of these countries the eligibility criteria tended to be stricter than The European League Against Rheumatism (EULAR) recommendations and were not following the treat-to-target recommendations.[15 16]

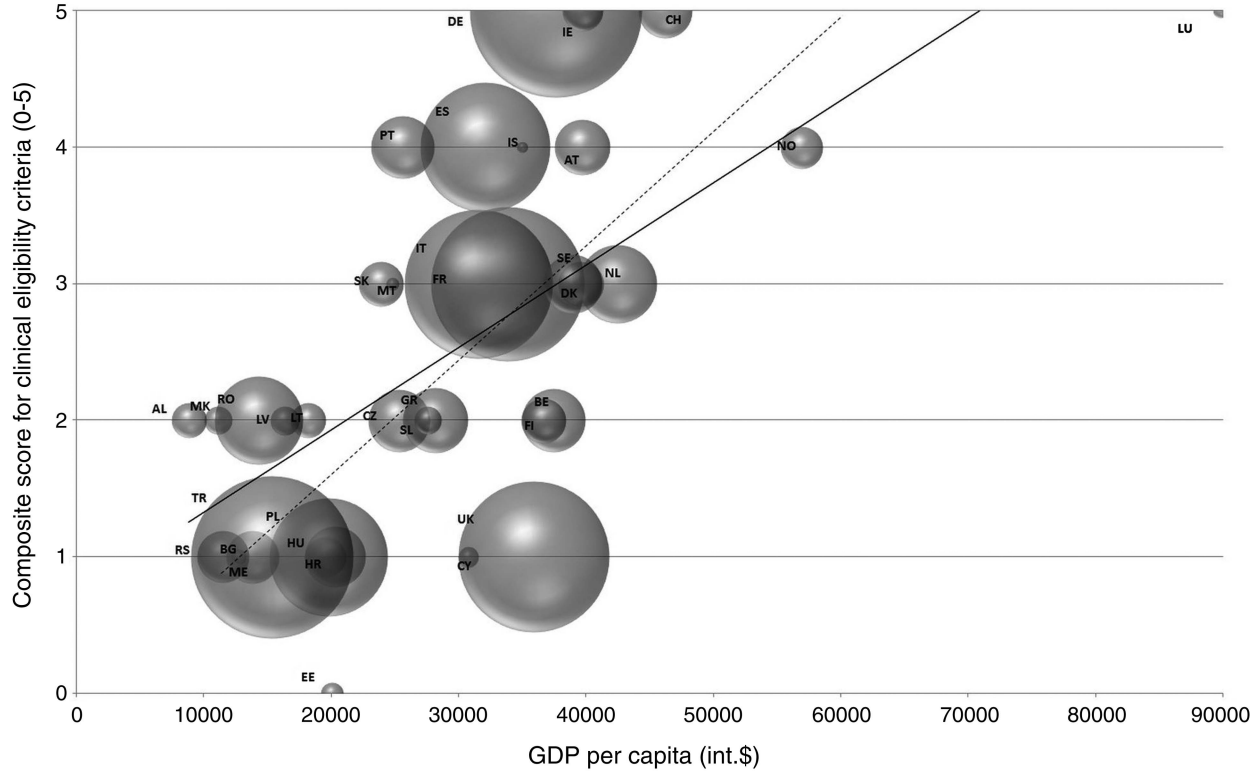

Figure 2 Composite score for restrictiveness of clinical criteria (0–5) and GDP per capita (int/$), n=36. Size of the bubble is proportional to the population size of each country. Dashed trend line is added to show the linear trend if without data from Luxemburg, which can be considered an outlier GDP, gross domestic product.
AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; HR, Croatia; CY, Cyprus; CZ, Czech Republic; EE, Estonia; FI, Finland; FR, France; DE, Germany; DK, Denmark; GR, Greece; HU, Hungary; IS, Iceland; IE, Ireland; IT, Italy; LV, Latvia; LT, Lithuania; LU, Luxemburg; MK, Macedonia; MT, Malta; ME, Montenegro; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; SK, Slovakia; SL, Slovenia; ES, Spain; SE, Sweden; CH, Switzerland; TR, Turkey; UK, United Kingdom.

Table 4 Correlations between clinical eligibility criteria, national indicators of socioeconomic development and health status indicators of patients with RA in 36 countries of the European Region (27 countries of the European Union)*

	Indicators of socioeconomic welfare			Health status indicators of patients with RA						Uptake of bDMARDs
Clinical eligibility criteria	GDP per capita (int.$) n=27–36†	Median income (int.$) n=27–30†	Total health expenditure per capita (int.$) n=27–36†	DAS28 n=17–20†	TJC n=17–20†	MD Global VAS n=17–20†	HAQ n=17–20†	PT global VAS n=17–20†	ESR n=17–20†	bDMARDs ever, % of patients n=16–18†
Minimum disease duration (months)	−0.41 (−0.48)	−0.50 (−0.45)	−0.34 (−0.4)	0.48 (0.37)	0.47 (0.33)	0.48 (0.38)	0.51 (0.42)	0.33 (0.24)	0.33 (0.32)	−0.58 (−0.60)
Level of DAS28	−0.61 (−0.49)	−0.60 (−0.55)	−0.64 (−0.56)	0.36 (0.29)	0.26 (0.25)	0.36 (0.35)	0.41 (0.36)	0.27 (0.24)	0.40 (0.33)	−0.31 (−0.21)
Number of sDMARDs to be failed	−0.56 (−0.47)	−0.46 (−0.37)	−0.54 (−0.41)	0.17 (0.13)	0.19 (0.22)	0.18 (0.21)	0.23 (0.19)	0.11 (0.05)	0.28 (0.15)	−0.70 (−0.68)
Composite score for clinical eligibility criteria (0–5)	0.70 (0.63)	0.67 (0.59)	0.72 (0.66)	−0.46 (−0.39)	−0.42 (−0.42)	−0.45 (−0.46)	−0.52 (−0.46)	−0.33 (−0.27)	−0.48 (−0.40)	0.79 (0.72)

*First value corresponds to Spearman correlation between both variables in all the 36 countries and the second value refers to the same correlation but within those countries that are from the European Union.
†n corresponds to the minimum and maximum number of countries from which there were data for each of the correlations.
bDMARD, biologic disease-modifying antirheumatic drug; DAS28, disease activity score with 28-joint assessment; ESR, erythrocyte sedimentation rate; GDP, gross domestic product; HAQ, Health Assessment Questionnaire; MD, medical doctor; PT, patient; RA, rheumatoid arthritis; sDMARDs, synthetic disease-modifying antirheumatic drugs; TJC, tender joint count; VAS, Visual Analogue Scale.

The present study expands on the existing knowledge. First, 46 countries were surveyed covering nearly all European Region, thus providing more comprehensive picture regarding the regulations of prescriptions of bDMARDs as compared with previous studies.[6 17] Second, geographic variations in criteria regulating initiation of a first biologic were seen in their relation to countries' socioeconomic welfare, which expanded on study previously reported by Pease *et al*.[17]

Within the limitations of availability and generalisability of data on medication uptake and RA health status across countries, our findings are alarming as stricter clinical eligibility criteria seem to also be associated not only with lower uptake of biologics, but also with higher disease activity, thus suggesting that principles of equitable heathcare systems might be undermined within Europe. This finding was similar in EU and non-EU countries.

The study has some limitations. First, data were reported by one expert per country and we could not review the full texts of regulations (often published in local language only). However, contact persons were asked to clarify and check the results. Second, data on the health status and uptake of bDMARDs were only available from a single study conducted between 2005 and 2008 in a limited number of countries.[5] Nevertheless, to our knowledge it represents the best available international data on health status in patients with RA. We recognise that a large number of factors have to be considered in order to understand the relation between eligibility criteria and uptake of bDMARDs or health outcomes and many were not assessed in our study. First, the development of the composite score used to compare the restrictiveness of the criteria for initiation of a first bDMARD was not data-driven and should be interpreted with caution. It may be a line of further research to develop a validated tool to monitor the restrictiveness of criteria across countries in relation to health outcomes, which would inform policy makers in defining the major cut-off points. Next, the results do not take into account the regional variations that can exist within the countries.[18 19] However, we believe that presented data do provide a valuable insight into the patterns in eligibility for biologic treatment within Europe and formulate challenges for further research. Last but not the least, it should be emphasised that formal prescription requirements do not necessarily reflect the actual practice. Adherence to requirements is a question for further research, including the relevant question whether within countries specific barriers or facilitators can be identified at the level of the organisation and financing as well as at the level of prescribers and patients.[20 21]

In contrast to the situation in RA, national regulations in ankylosis spondylitis (AS) were consistent with the recommendations from the Assessment of SpondyloArthritis international Society (ASAS) and EULAR.[22] One of the reasons may be limited conservative treatment options in AS that result in less discussion on the clinical indication to start a biologic. Also, AS is less prevalent and its impact on budget is of less concern for policy makers. Furthermore, the existence of a specific society for AS (ASAS) that makes efforts towards spreading knowledge can play a role. Strengthening of the role of EULAR in aligning the national guidelines according to the EULAR recommendations and helping countries to understand barriers against adapting guidelines might be essential on the way to equity worldwide and this area of research is growing.[23]

In conclusion, the socioeconomic welfare of a country is associated with the strictness of eligibility criteria stated in national regulations to prescribe reimbursed treatment with bDMARDs. This becomes unfair when universal right to healthcare is

increasingly influenced by pure financial considerations, and patients in countries with lower budgets have stricter clinical requirements to initiate a treatment that would be clinically recommended at earlier stage. However, the problem is complex and has to be treated within the national priorities on public health agenda.

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