Chapter 5

Assessment of global disease activity in RA by patients and physicians: differences across countries in the METEOR database

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ABSTRACT

Objective

To compare the differences between patient (Pt) and physician (Ph) global disease activity score (GDA) within and across 13 countries in the Measurement of efficacy of Treatment in the 'Era of outcome' in Rheumatology (METEOR) database.

Methods

Data from METEOR were used to compare PtGDA and PhGDA, scored independently on a 100 mm visual analogue scale (VAS) from 0 (best possible) until 100 (worst possible), in 23.117 visits in 5.709 anonymized patients during the period between 2008 and 2012. Linear Mixed Models (LMM) were used to model mean differences between PtGDA and PhGDA in 13 countries (Brazil, Czech, France, Ireland, Italy, Latvia, Mexico, the Netherlands, Pakistan, Portugal, Spain, United Kingdom and the United States), adjusted for differences in DAS28. Generalized Estimating Equation (GEE) were used to model differences (>20mm) between PtGDA and PhGDA score as the outcome and countries as determinants, adjusted for DAS28.

Results

Mean difference between PtGDA and PhGDA score varied by country, from -2mm (physician scores higher) in Mexico to +14mm (patient scores higher) in Brazil. 'Country' was a significant determinant of the difference between PtGDA and PhGDA score, independent of differences in DAS28. With Netherlands as reference, PtGDA and PhGDA scores for individual patients differ significantly in almost all (n=10) countries, with the exception of France and Spain.

Conclusion

Differences between patients' and physicians' assessment of global disease activity vary across the countries. Influence of country must be taken into account when interpreting discordances between the patient's and the physician's assessment of global disease activity in RA.

INTRODUCTION

The use of patient reported outcomes is valuable when measuring status and change in health care.[1] Both the patient's perception and the physician's assessment of the disease play an important role in making treatment decisions and achieving therapeutic goals. However, discordances in the patient's and physician's assessment of health status may adversely affect patients care.[2-5] In rheumatoid arthritis (RA), the visual analogue scale (VAS) is used to rate global disease activity (GDA) on a scale from 0 to 100 millimeter (0 representing best, 100 representing worst). The VAS can be used either as a patient reported outcome (patient GDA, PtGDA) or as a physician reported outcome (physician GDA, PhGDA).

Previous studies have shown that patients and rheumatologists may differ in rating their impression on a GDA scale. These studies have suggested that patients tend to score GDA higher than their physicians, which suggests that patients and physicians take into account different factors when rating global disease activity.[6-12]

However, it is not well known whether the country in which patient and physician live influences the discrepancy in GDA assessment. Differences between PtGDA and PhGDA may for example be dependent on the language used by patient and physician, but also on differences in the physician-patient relationship across different cultures.[13,14]

The Measurement of efficacy of Treatment in the 'Era of outcome' of Rheumatology (METEOR) initiative has developed an online database that provides an easy to use program to register clinical data of RA patients monitored in daily practice. Anonymized data uploaded by participating rheumatologists in 13 countries on three continents were used to compare the mean differences between PtGDA and PhGDA within and across the Netherlands and 12 other countries on three continents.

METHODS

A cross-sectional study was conducted to investigate the influence of country on the difference between PtGDA and PhGDA. We used data from the METEOR database, a worldwide online tool for disease monitoring in RA. Clinical data on anonymized patients with newly diagnosed and patients with established RA of 26 countries and 81 hospitals are collected in this central database until 6 July 2012. A more detailed description of the METEOR database was published previously.[11,15]

For the current analysis, we selected countries for which at least 100 patient visits had been recorded in METEOR between 1 January 2008 and 6 July 2012: Brazil, Czech Republic, France Ireland, Italy, Latvia, Mexico, the Netherlands, Pakistan, Portugal, Spain, United Kingdom and the United States. There were 23.117 visits of 5.709 patients, ranging from 108 to 6.718 visits per country and from 1 to 29 visits per patient containing both PtGDA and PhGDA scores. Patients rated the PtGDA and physicians rated the PhGDA on a 100mm VAS scale. The order in which the PtGDA and PhGDA were to be scored was not specified.
A difference of ≥20mm between PtGDA and PhGDA score was chosen as cut-off value for clinically relevant differences between patient and physician score and was dichotomously (yes versus no) evaluated.[11] Country was defined as a categorical variable with Netherlands as a reference category, because it has provided the highest number (n=6.272) of patient data. We adjusted for DAS28 (based on four variables) status at the time of the visit, since disease activity can be a determinant of a difference between PtGDA and PhGDA.[10,11] 'Short' or 'long' disease duration was categorized according to the median disease duration of 2 years in this study and definitions in previous studies.[16,17]

Statistical analysis

A Bland and Altman plot was performed to visualize the differences between PtGDA and PhGDA among countries. A multilevel approach was followed to allow for the correlation between multiple visits within a subject. Mean GDA (the average of PtGDA and PhGDA) and the mean differences between PtGDA and PhGDA for each country were estimated using linear mixed models (LMM). LMM were also used to estimate the mean difference between PtGDA and PhGDA for gender and for disease duration stratified per country. Generalized estimated equations (GEE) were used to model a difference of 20 mm between PtGDA and PhGDA, with 'country' as a determinant and the Netherlands as reference category, adjusted for DAS28. Software program SPSS version 17.0 was used for the analyses and p-values smaller than 0.05 were considered statistically significant.

RESULTS

The numbers of PtGDA and PhGDA assessments (respectively) per country were as follows: Brazil: 1.220 and 1.195; Czech: 487 and 460; Spain: 238 and 244; France: 522 and 412; United Kingdom: 1.730 and 148; Ireland: 656 and 534; Italy: 3.987 and 3.747; Latvia: 135

and 110; Mexico: 570 and 563; Netherlands: 17.923 and 6.804; Pakistan: 267 and 264, Portugal: 8.772 and 5.966; and United States: 2.025 and 1.939. Overall, patients scored GDA higher than physicians, resulting in an overall mean difference (mean (95% CI)) between PtGDA and PhGDA of +9 mm (95% CI: 8.9 to 9.4) (Patients score higher). Figure 1 shows the distribution of mean differences between PtGDA and PhGDA per country as a function of mean GDA in that country. The difference in scores between patient and physician was highest in Brazil (+14 (12.5 to 16.2) mm) while Mexico was the only country in which average PtGDA was lower than the average PhGDA (-1 9 (-4.8 to +2.6) mm).

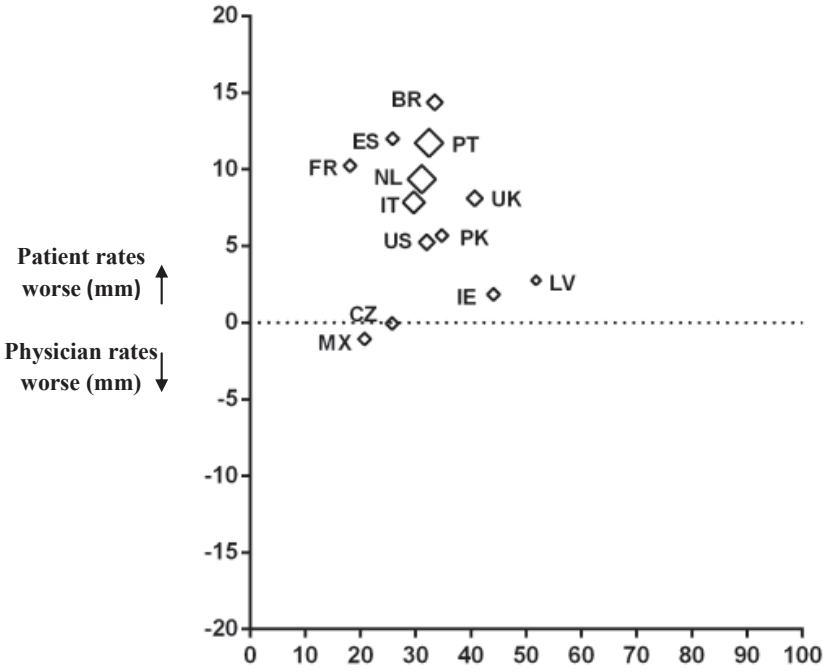

Figure 1. Crude Mean difference (mm) between patient (PtGDA) and physician (PhGDA) global disease activity score per country.

BR=Brazil, ES=Spain, PT=Portugal, NL=Netherlands, IT=Italy, US=United States, UK=United Kingdom, PK=Pakistan, CZ=Czech, MX=Mexico, FR=France, IE=Ireland, LT=Latvia. The size of the bubble is a reflection of the number of available visits.

Latvia was the country with the highest mean values of both patient and physician GDA scores (51.8 (45.6 to 58)). Absolute mean values of PtGDA and PhGDA were lowest in Mexico (20.7 (15.2 to 26.2)) and in France (18.1 (15.2 to 21.1)). The differences between PtGDA and PhGDA stratified for males and females are shown in table 1.

Table 1. Mean difference (mm) between patient (PtGDA) and physician (PhGDA) global disease activity score for men and women stratified by country

	PtGDA minus PhGDA		
Country	**Male**	**Female**	**p-value**
	Mean (95% CI)	**Mean (95% CI)**	
Brazil	14.1 (6.7 to 21.4)	14.4 (11.5 to 17.3)	0.93
Czech	-1.4 (-5.7 to 3.0)	0.65 (-2.5 to 3.8)	0.46
Spain	7.9 (1.0 to 14.7)	12.9 (9.3 to 16.5)	0.20
France	7.6 (3.3 to 11.8)	11.27 (8.9 to 13.7)	0.14
United Kingdom	5.4 (3.3 to 7.6)	8.9 (7.7 to 10.1)	<0.01
Ireland	1.8 (-1.5 to 5.1)	1.6 (-0.3 to 3.5)	0.93
Italy	5.8 (3.9 to 7.6)	8.0 (7.1 to 8.9)	0.04
Latvia	-1.6 (-9.6 to 6.6)	3.9 (1.1 to 6.7)	0.12
Mexico	-1.3 (-9.9 to 7.2)	0.2 (-1.3 to 1.7)	0.73
Netherlands	7.7 (6.8 to 8.7)	10.2 (9.5 to 10.8)	<0.01
Pakistan	6.5 (-2.1 to 15.0)	5.7 (2.17 to 9.2)	0.86
United States	4.7 (2.2 to 7.1)	5.4 (4.0 to 6.8)	0.63
Portugal	10.2 (8.1 to 12.2)	12.0 (11.2 to 12.9)	0.10
Overall	**6.9 (6.2 to 7.6)**	**9.3 (8.9 to 9.7)**	**<0.01**

CI=confidence interval.

Physicians rated disease activity on average 6.9 (6.2 to 7.6) mm lower than male patients and 9.3 (8.9 to 9.7) mm lower than female patients. We were not informed about the gender of the

rating rheumatologist. The overall difference between men and women was statistically significant ($p<0.01$). Within countries, the difference between physicians and female patients is numerically higher than the difference between physicians and male patients. This was true for all countries except Ireland and Pakistan. These discrepancies reach statistical significance for the UK, the Netherlands and Italy. The overall mean difference between PtGDA and PhGDA also differed significantly for patients with 'short' vs. those with 'long' disease duration (table 2).

Table 2. Mean difference (mm) between patient (PtGDA) and physician (PhGDA) global disease activity score for disease duration in years stratified by country

	PtGDA minus PhGDA		
Country	**Dis Dur ≤2 year, mean (95% CI)**	**Dis Dur >2 year, mean (95% CI)**	**p-value**
Brazil	11.4 (6.0 to 16.9)	15.9 (12.6 to 19.1)	0.12
Czech	-1.2 (-4.5 to 3.0)	-	-
Spain	8.9 (0.5 to 17.3)	12.2 (6.6 to 17.7)	0.52
France	4.7 (-4.5 to 13.8)	10.7 (8.4 to 12.9)	0.21
United Kingdom	3.7 (-0.1 to 7.5)	9.0 (6.8 to 11.1)	0.02
Ireland	1.0 (-2.3 to 4.2)	3.50 (0.8 to 6.2)	0.23
Italy	7.1 (5.6 to 8.6)	6.7 (5.8 to 7.6)	0.58
Latvia	-0.5 (-6.3 to 5.3)	2.8 (-5.2 to 10.7)	0.47
Mexico	-1.8 (-4.3 to 0.9)	-	-
Netherlands	9.8 (7.8 to 11.8)	8.8 (7.5 to 10.0)	0.37
Pakistan	9.1 (3.4 to 14.7)	4.3 (0.3 to 8.4)	0.18
United States	8.2 (5.5 to 10.9)	2.4 (0.4 to 4.4)	<0.01
Portugal	11.2 (8.8 to 13.5)	12.4 (11.5 to 13.3)	0.31
Overall	**6.9 (6.0 to 7.9)**	**9.1 (8.6 to 9.6)**	**<0.01**

CI=confidence interval. Dis Dur=disease duration

Patients with a short disease duration scored on average 6.9 (6.0 to 7.9) mm higher than their physician, while patients with a longer disease duration scored on average 9.3 (8.9 to 9.7) mm higher than their physician ($p<0.01$) for the difference between short and long disease duration). Within the countries, significant differences between short and long disease duration in PtGDA versus PhGDA score were present in the UK and in the United States. In the UK, differences between PtGDA and PhGDA were smaller when disease duration was short (3.7, (-0.1 to 7.5) mm) compared to long (9.0 (6.8 to 11.1) mm). In the United States the opposite was observed: differences between PtGDA and PhGDA were on average smaller when disease duration was long (2.4 (0.35 to 4.4) mm), as compared to short (8.2 (5.5 to 10.9) mm).

Table 3. Difference (20mm) between patient (PtGDA) and physician (PhGDA) global disease activity score (yes/no), comparison between countries*

	Difference present (n=6.190) versus difference absent (n=14.684)			
Country, visits (n)	PtGDA higher	PhGDA higher	OR (95% CI)	p-value
Brazil (958)	342 (36)	71 (7)	1.63 (1.33 to 2.00)	<0.01
Czech (457)	60 (13)	46 (10)	0.70 (0.53 to 0.93)	0.01
Spain (193)	47 (24)	2 (1)	0.92 (0.62 to 1.37)	0.69
France (396)	106 (27)	2 (0)	1.18 (0.91 to 1.54)	0.22
United Kingdom (1.076)	221 (21)	28 (3)	0.61 (0.51 to 0.73)	<0.01
Ireland (475)	59 (13)	39 (8)	0.59 (0.46 to 0.76)	<0.01
Italy (3.414)	742 (22)	99 (3)	0.75 (0.65 to 0.88)	<0.01
Latvia (105)	6 (6)	5 (5)	0.17 (0.07 to 0.40)	<0.01
Mexico (445)	31 (7)	30 (7)	0.37 (0.26 to 0.52)	<0.01
Pakistan (160)	44 (28)	23 (14)	1.70 (1.13 to 2.56)	0.01
Portugal (5.526)	1837 (33)	207 (4)	1.35 (1.22 to 1.50)	<0.01
United States (1.397)	280 (20)	77 (6)	0.85 (0.72 to 1.00)	0.05

* Reference category= Netherlands (n visits=6.272), corrected for DAS28 (Disease Activity Score for 28 joints), n=number, CI=confidence interval, OR=Odds Ratio.

In databases of the Czech Republic and Mexico, only patients with short disease duration were recorded in the METEOR database. In both of these countries, physicians scored global disease activity on average higher than the patients. Table 3 shows, by country, the likelihood (in odds ratios) that a difference in GDA between physician and patient of more than 20mm was found, relative to the Netherlands corrected for DAS28. Among RA patients from the Netherlands who enrolled in the METEOR database, 28% of the visits showed a discrepancy of at least that magnitude. In Brazil, Pakistan and Portugal the likelihood of a discrepancy of at least that magnitude was higher than in the Netherlands, whereas in the UK, Ireland, Italy, Latvia, Mexico, Czech Republic and the United States this likelihood was lower. Table 3 also shows the number of times that the patient scored higher (20mm) than the physician and vice versa per country. In all countries it was more frequent that PtGDA is higher (20mm) than PhGDA.

DISCUSSION

The analyses described in this study report the influence of country of residence on the comparison of patients' and physicians' assessments of global disease activity in RA. While we have investigated already such differences in the Netherlands only,[11] we now have described patterns in 13 different countries all over the world. In these countries, the patient usually rated his or her global disease activity to be worse than did the assessing physician.
With the Netherlands as reference, we found clinically relevant differences between physicians' and patients' ratings in almost all countries, except for France and Spain. The magnitude to which these patient-reported and physician-reported GDA deviates varies per country. Gender differences seem to contribute, reaching statistical significance in Italy, Netherlands and the United Kingdom. The relationship between disease duration and patient/physician discrepancy is more heterogeneous across countries but may also contribute to overall differences between countries.

Since DAS28 is likely to be associated with a difference between PtGDA and PhGDA, we adjusted for DAS28. Even after correction, country of residence appeared to be a determinant of discrepancy in assessment of global disease activity between patient and physician, making it more likely that there is a true country-specific influence. Our finding that the difference between PtGDA and PhGDA varies by country has important implications. Multi-national observational studies, in which patient-reported outcomes are analyzed, may be

interpreted in the context of cultural differences between countries, or alternatively in the context of ethnicity.[18] This is in line with findings in some previous studies. It has been shown that the disease burden by patients differs per country.[19-22] Several studies have demonstrated a large variation between countries in the prevalence of low back pain and chronic pain.[19] Gureje et al. showed that the prevalence of chronic pain is relatively high in South American countries, such as Brazil, compared to Asian countries.[19] Besides, RA-patients may have concomitant fibromyalgia syndrome that may explain excess of pain.[24,25] In our study, Brazil was the country with the largest differences between patient's and physician's GDA score. Patients scored on average 14 mm higher than their physician, which might share similar origins with the higher prevalence of chronic pain in Brazil.[26] Along similar lines, patients from the Mediterranean have been shown to report more pain than patients living in Northern and Western Europe.[27] The findings of our study show similar trends: a greater discrepancy between PtGDA and PhGDA, resulting from patients scoring higher disease activity than their physicians, was observed in Portugal and Spain than in Ireland and the United Kingdom. These differences in patient-reported vs physician-assessed disease burden is difficult to explain. Cross-cultural differences may play a role, just as ethnic differences. Alternatively, different expectations about the disease RA between physicians and patients may play a role.[28]

In three countries we have also found associations between gender and the differences in GDA scores between patients and their physicians. In the United Kingdom, the Netherlands and Italy the discrepancy between PtGDA and PhGDA was significantly higher for women than for men, while the direction of the difference was the same in males and females (patients scored higher than physicians). In each of the other 10 countries these gender differences were not statistically significant, but were in the same direction in all countries except Ireland and Pakistan. Pooling the data of all 13 countries resulted in statistically significant gender associations. These associations pertained to small effects (differences of +2mm) but at least suggest that the country where patient and physician reside should be taken into account when comparing gender differences in GDA assessment. We should further not rule out measurement error as potential explanations when looking at such small differences. Previous studies have also suggested gender differences with regard to patient reported outcomes in multiple countries. In general, female patients often report more pain and higher disease activity compared to men, both within- and across countries.[29]

We found longer disease duration to be associated with different patient's and physician's GDA assessment in two countries; The United States and the United Kingdom. Further

studies should elucidate if this association is true (and requires explanation) or based on statistical artifacts. As said, pooling the data of all 13 countries yielded a mean difference of only 2 mm, which appears not to be very important, especially since the differences within countries are heterogeneous.

A strength of this study was the availability of a large number of patients and visits, which increases the power of the study. A limitation is the cross-sectional nature of the study, which does not allow to assess cause and effect. In addition, PtGDA and PhGDA were not assessed independently, which may have influenced the differences in scores between countries. Also, the patients entered into the METEOR database do not represent a random sample of the population of RA patients in each country. The number of visits available for analysis varied by country from 105 to 6.200, which might result in less reliable conclusions drawn from data collected in countries in which there were only small numbers of visits. Furthermore, data of physical functioning and comorbidities, which may also influence the perception of GDA (by patient and physician), were often not reported in METEOR and could not be adjusted for. A last limitation to be mentioned is that PtGDA and PhGDA in this database with data obtained in regular clinical practice (without pre-specified protocol) may not have been obtained independently; the physician most often must have been aware of the patient's judgement when giving his own judgement. This is inherent to common clinical practice and, even though it may decrease rather than increase a difference between PtGDA and PhGDA, precludes a robust scientific explanation for the observed differences.

In conclusion, differences between patient's and physician's assessment of global disease activity are partly dependent on the country in which the patient and the physician reside. In some countries, these differences are related to gender and disease duration, while this is not so obvious in others. Our findings may have implications for generalizing international data. There may be restrictions as to what extent we can combine and interpret data obtained in different countries. The influence of country must be further investigated and taken into account when interpreting discordances between the patient's and the physician's assessment of global disease activity in RA and perhaps also when incorporating these scores into recommendations regarding decision algorithms on medication use, such as Treat-to-Target strategies.

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