Are rheumatologists adhering to the concepts *window of opportunity* and *treat-to-target*? Earlier and more intense disease-modifying anti-rheumatic drug treatment over time in patients with early arthritis in the PEARL study

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Abstract

Objective

To analyse changes over time in the treatment with disease modifying anti-rheumatic drugs and biological therapies prescribed to patients from an early arthritis register and whether these changes had an impact on their outcome.

Methods

This was a longitudinal retrospective 2-year study based on data collected in the PEARL study. The population was clustered in three groups depending on year of symptoms onset (2000-2004, 2005-2009, 2010-2014). Intensity of disease-modifying anti-rheumatic drug treatment was calculated and the percentage of patients receiving biological therapy during the first 2-year follow-up was collected. Disease activity and remission at the end of follow-up, as well as radiological progression were the outcomes analysed. Multivariable analyses were fitted to determine which variables including the three period times were associated with the outcomes.

Results

A significant increase in treatment intensity was observed in patients with undifferentiated arthritis, getting closer to that prescribed to patients fulfilling the 1987 RA criteria at the last period studied (2010-2014). This finding was associated with a significantly higher percentage of patients in remission and lower progression of the erosion component of the Sharp van der Heijde score.

Conclusion

During the last 15 years, the treatment of patients with early arthritis in our hospital has been progressively increased and it has been associated with significantly better outcomes.

Key words
early arthritis, rheumatoid arthritis, outcomes, treat-to-target, PEARL

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Introduction

The management of rheumatoid arthritis (RA) has improved over the last 15 years, leading to a better control of the disease (1-3). The availability of biological therapies (BT) at the beginning of this century represented a revolution in the capability to improve RA disease activity and to halt radiological progression (4). In addition, intensification of chemical disease-modifying antirheumatic drugs (DMARDs) through the *treat-to-target* strategy have also greatly contributed to a better control of disease activity (5).

On the other hand, the concept *window of opportunity* has been definitively confirmed (6) after subtle evidences at the end of the last century (7). This information has driven to the proposal of earlier intervention, leading to new RA classification criteria (8) and even suggesting that some patients must be treated even before RA diagnosis (9, 10) in order to avoid progression of the disease and eventually achieve drug free-remission.

Despite all these advances, a significant proportion of patients still maintain high levels of disease activity, thus supporting the search for new drugs and biomarkers to early predict unresponsiveness. However, this failure could also be due to low adherence to all these strategies, as the uptake of any guideline takes time and adaptation to the context. It is known that physicians' adherence to treatment strategies in early RA is associated with improved remission rates and even to lesser use of biologics (11), and that low adherence may be related to disagreement with disease activity measurements or dissatisfaction with the level of disease suppression (12, 13). Previous studies have analysed on a one-to-one basis whether physicians were adherent to these strategies, *e.g.* whether a treatment should have been started or not, or combined, or intensified. We, herein, propose an additional approach to evaluate the uptake of treatment strategies by determining the change in treatment intensity over time in the early phases of the disease. Thus, the objective of this work was to analyse whether treatment with DMARDs and BT have changed over time in an early arthritis register.

Methods

Design and patients

This is a longitudinal retrospective two-year study based on data collected in the PEARL (Princesa Early Arthritis Register Longitudinal) study. The PEARL study is populated with incident cases of patients with 1 or more swollen joints for less than a year referred to the Early Arthritis clinic at Hospital La Princesa, Madrid. Patients with gouty arthritis, septic or viral arthritis, osteoarthritis, spondyloarthritis, or connective tissue diseases diagnosed during the follow-up period were excluded from this study. Only those patients fulfilling 1987 RA criteria (14) and those considered undifferentiated arthritis (15) after 24 months of follow-up were included in this work. The register includes 5 structured visits (baseline, 6, 12, 24 and 60 months) in which socio-demographic, clinical, laboratory, therapeutic, radiological data and biological samples are systematically collected by protocol.

It is important to point out that there is no pre-established therapeutic protocol in PEARL, so the decision on when and how to treat the patients relies on each of the 11 responsible physicians from the rheumatology department during the normal follow-up. The register specific evaluation visits are performed by two rheumatologist (AMO, IG-A) in order to get a more accurate clinical evaluation, especially regarding joint counts. A more detailed description of PEARL study has been published (16). The register started in 2000 and it is still ongoing, but the last patients included in this study were those with the 24 months follow-up visit performed by December 2016.

PEARL study is conducted according to the principles expressed in the Helsinki Declaration of 1983 and it was approved by the Research Ethics Committee of Hospital Universitario La Princesa (PI-518). All patients signed a written consent at study entry.

Variables

PEARL protocol establishes a careful collection of information about treatment with DMARDs, either chemical or biological. Time to first DMARD was estimated since the date of symp-

Table I. Characteristics of the populations of PEARL study in the three periods of time analysed.

	2000-2004 (n=148)	2005-2009 (n=167)	2010 -2014 (n=141)	*p*-value
Female, n (%)	111 (75.0)	136 (81.4)	113 (80.1)	0.344
Age (years; p50 [IQR])	50.6 [38.5-64.7]	54.2 [44.4-68.7]	58.7 [48.2-69.5]	0.001
Smoking, n (%)				
Never	88 (62.9)	87 (55.8)	74 (52.9)	0.099
Ever	23 (16.4)	29 (18.6)	39 (27.9)	
Current	29 (20.7)	40 (25.6)	27 (19.3)	
Disease duration (months; p50 [IQR])	6.6 [4.6-9.8]	5.2 [2.9-8.2]	4.1 [2.6-7.1]	<0.001
RF, n (%)	67 (45.3)	88 (52.7)	84 (59.6)	0.052
ACPA, n (%)	52 (35.6)	86 (53.4)	76 (53.9)	0.002
Baseline 2010 RA criteria, n (%)	88 (59.5)	117 (70.1)	96 (68.1)	0.115
Two-year 1987 RA criteria, n (%)	103 (69.6)	113 (67.7)	106 (75.2)	0.335
Undifferentiated arthritis after 2 years, n(%)	45 (30.4)	54 (32.3)	35 (24.8)	0.335
Baseline DAS28 (p50 [IQR])	4.2 [3.2-5.6]	4.9 [3.6-5.7]	4.3 [3.3-5.5]	0.040
Baseline HAQ (p50 [IQR])	0.875 [0.5-1.625]	1 [0.625-1.625]	0.875 [0.5-1.75]	0.441

n: number; IQR: interquartile range; ACPA: anti-citrullinated protein antibodies; p50: 50th percentile or median; SD: standard deviation; BMI: body mass index; RA: rheumatoid arthritis; RF: rheumatoid factor; DAS28: Disease Activity Score based on a 28-joint count; HUPI: Hospital Universitario La Princesa Index; HAQ: Health Assessment Questionnaire.

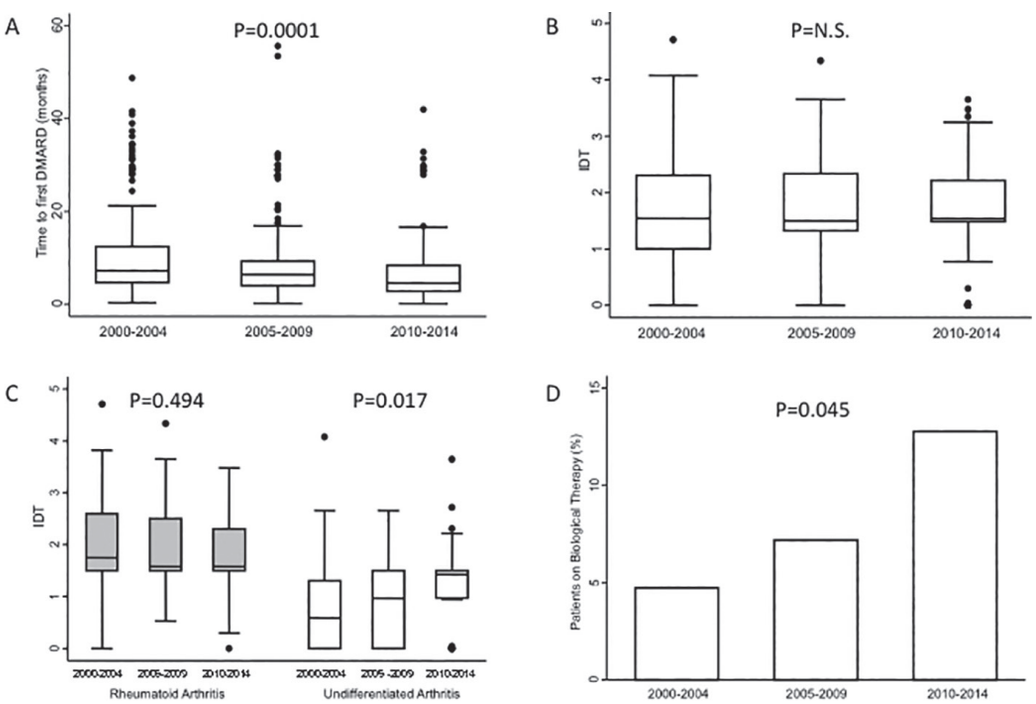

Fig. 1. Prescription of treatment in patients from PEARL study depending on the year of symptoms onset.
A: Time to first disease modifying anti-rheumatic drug (DMARD) since symptoms onset.
B: Intensity of DMARD treatment (IDT; see *Methods* for definition);
C: Differences in IDT between patients fulfilling 1987 ACR rheumatoid arthritis criteria (grey bars) and those considered undifferentiated arthritis (white bars);
D: Percentage of patients prescribed with biological therapy. At panels A to C data are shown as the median of time (A) or IDT (B, C) (line inside the boxes) and the percentiles 25, 75 (lower and upper lines of the boxes, respectively), 10 and 90 (end points of the lines outside the boxes).
Circles represent outliers.

toms onset as reported by the patient. To assess the intensity of DMARD treatment (IDT) we have previously described this variable calculated as the sum of the number of days on treatment with any DMARDs synthetic or biologic, weighted by the type of DMARD (1x antimalarials, 1.5x methotrexate, sulphasalcine, leflunomide, cyclosporine A and gold salts, 2x biological therapy), and normalised by the number of days between the baseline and 24 months visits (17). In summary, an IDT score of 1 would mean that the patient was treated with monotherapy of antimalarials during all days along the first two years of follow-up or 75% of the days with monotherapy of methotrexate, leflunomide or sulphasalacine, or 50% of the days with monotherapy of a biologic. The range of values for this variable is 0 to 5, being 4.7 the highest value reached in the population studied in this work. In addition, the use of biological therapy during the first 24 months of follow-up was registered.

Supplementary Table I. Use of non-biologic disease-modifying anti-rheumatic drugs in PEARL study in the three periods of time analysed .

	2000-2004 (n=148)	2005-2009 (n=167)	2010 -2014 (n=141)	*p*
Methotrexate, n (%)	108 (73)	118 (71)	120 (85)	0.011
Leflunomide, n (%)	51 (34'5)	57 (34)	49 (35)	0.967
Antimalarial, n (%)	53 (36)	42 (25)	24 (17)	0.001
Sulphasalazine, n (%)	29 (20)	9 (5)	6 (4)	<0.001
Gold salts, n (%)	9 (6)	2 (1)	0 (0)	0.002
Cyclosporine A, n (%)	3 (2)	0 (0)	0 (0)	0.334

Table II. Variables associated with disease activity at the end of follow-up.

	HUPI		DAS28		Remission (SDAI<3.3)	
	β coeff. (95% CI)	*p*	β coeff. (95% CI)	*p*	OR (95% CI)	*p*
Age at DO						
<45	Ref.	-	Ref.	-	Ref.	-
45-65	0.62 (-0.04 – 1.27)	0.066	0.34 (0.03 – 0.65)	0.029	0.64 (0.37 -1.11)	0.116
>65	0.65 (-0.08 – 1.38)	0.080	0.16 (-0.18 – 0.50)	0.369	0.49 (0.26 – 0.91)	0.023
Female	NI	N.S.	0.61 (0.30 – 0.91)	<0.001	0.49 (0.28 – 0.86)	0.012
Smoking	NI	N.S.	NI	N.S.	NI	NS
DD at baseline	NI	N.S.	NI	N.S.	NI	NS
RF	NI	N.S.	NI	N.S.	NI	NS
ACPA	0.54 (0.00 – 1.08)	0.048	NI	N.S.	NI	NS
DA at baseline						
Remision	Ref.	-	Ref.	-	Ref.	-
Low	0.54 (-0.42 – 1.49)	0.269	-0.01 (-0.55 – 0.54)	0.981	0.57 (0.25 – 1.29)	0.177
Moderate	1.26 (0.31 – 2.21)	0.010	0.56 (0.12 – 0.99)	0.012	0.39 (0.17 - 0.89)	0.025
High	1.39 (0.47 – 2.31)	0.003	0.86 (0.41 – 1.31)	<0.001	0.37 (0.17 – 0.84)	0.017
Year of symptom onset						
2000-2004	Ref.	-	Ref.	-	Ref.	-
2005-2009	-0.89 (-1.54 - -0.24)	0.007	-0.32 (-0.62 - -0.01)	0.042	2.03 (1.15 – 3.60)	0.015
2010-2014	-1.26 (-1.92 - -0.60)	<0.001	-0.55 (-0.86 - -0.24)	<0.001	2.09 (1.16 – 3.76)	0.014

HUPI: Hospital Universitario Princesa Index; DAS28: Disease Activity Score with 28 joint counts; SDAI: Simplified Disease Activity Index; coeff: coefficient; OR: odds ratio; DO: disease onset; Ref: reference; NI: not included in the final model because not significant (NS); DD: disease duration; RF: rheumatoid factor; ACPA: anti-citrullinated proteins antibodies; DA: disease activity. Multivariable analysis was performed through lineal regression for HUPI and DAS28 and through logistic regression for remission (see *Methods* for detailed information)

In order to analyse whether the intensity of treatment changed over time the total population was split in three subpopulations considering the year of symptoms onset: 2000–2004, 2005–2009 and 2010–2014. The main reason for deciding these periods was having a balanced number of patients in each group. Nevertheless, they also fit well with key events in the therapeutic management of RA during the last 15 years, since the first paper reporting the usefulness of tight control strategy appeared in 2004 (18) and the treat-to-target recommendations for RA management appeared in 2010 (19).

Clinical and laboratory data collected by protocol allowed us to calculate DAS28 (20), SDAI (21) and HUPI (22) in order to determine disease activity at each visit. Remission at two years of follow-up was established as SDAI≤3.3 (8).

In addition, hands and wrists x-rays were performed at baseline, 1- and 2-year follow-up and were assessed using the Sharp score with the van der Heijde modification (SHS; maximum erosion score 160 and maximum narrowing/subluxation score 120) (23) by an experienced evaluator (JI-C). The intra-class correlation coefficient was assessed by reading 10% of the radiographs twice and it was 0.99.

Statistical analysis

The descriptive analysis was performed by calculating the mean and standard deviation (SD) of quantitative variables with a normal distribution. The median and the interquartile range (IQR) were calculated for those variables with no normal distribution. Estimation of the proportions was used to describe qualitative variables. Anova test was applied to compare the means of variables with a normal distribution and Kruskall-Wallis test was used for variables that did not present normal distribution. The χ^2 test was used for qualitative variables.

Considering that there were differences in several characteristics of the three populations (Table I), we decided to perform multivariable analysis to determine whether these differences were biasing the association with the different outcomes analysed.

Disease activity at the end of follow-up was analysed through a multivariable linear regression by using generalised linear models using the command *glm* of Stata v. 12.1 (College Station, Tx, USA). Remission at the end of follow-up was analysed through a multivariable logistic regression by using the Stata command *logit*. Since the variable radiological progression was a zero-inflated variable, we decided to transform this continuous variable into a categorical variable with three options being 0 no radiological progression, 1 low radiological progression and 2 high radiological progression. The cut-off to discriminate between low and high radiological progression was considered the median value of those patients with radiological progression >0. Then, radiological progression was analysed through a multivariable ordered logistic regression by using the Stata command *ologit*. All those variables that were significantly different between the three populations were included in the initial model of these three multivariable analyses. Then, the final models were obtained through manual stepwise backward elimination of variables with $p>0.15$.

Results

Description of the 3 subpopulations of early arthritis patients

Table 1 shows the main characteristics of the three subpopulations by year of symptoms onset. The main differences between them are: a) a progressive increase in the age at disease onset; b) a steady decrease of disease duration at the baseline visit; and c) a lower percentage of anti citrullinated proteins

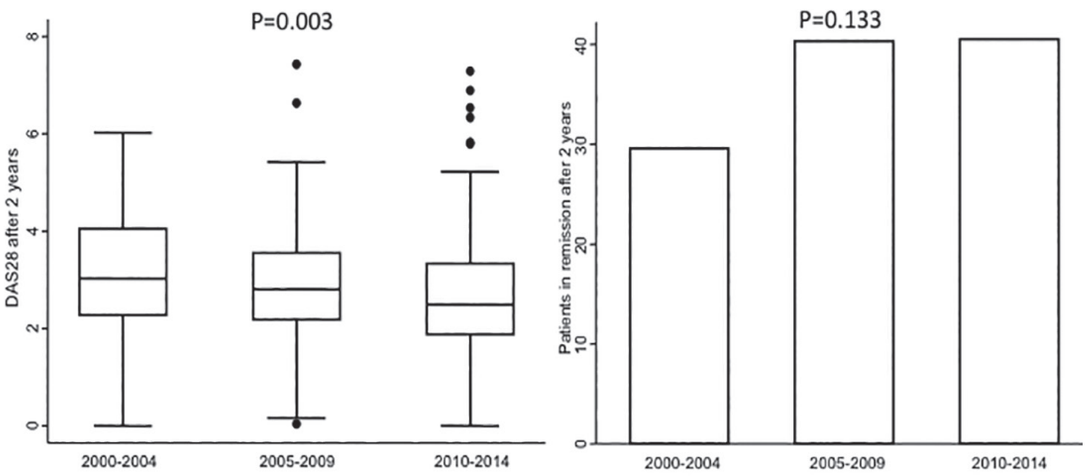

Fig. 2. Disease activity after 2-year follow-up in patients from PEARL study clustered by age of symptoms onset. Left panel shows the median value of DAS28 (line inside the boxes), as well as the percentiles 25, 75 (lower and upper lines of the boxes, respectively), 10 and 90 (end points of the lines outside the boxes). Circles represent outliers. Right panel shows the percentage of patient that reached remission defined as SDAI<3'3.

antibody (ACPA) positive patients in the first 5 years of the register.

Time to first DMARD and intensity of DMARD treatment

There was a significant decrease in the time to prescription of first DMARD (Fig. 1A), that was statistically significant either in patients classified as RA or undifferentiated arthritis (data not shown). However, the decrease in time to first DMARD was more impressive in patients with undifferentiated arthritis.

We did not observe any differences in the median IDT score by year of symptom onset (Fig. 1B). However, the percentile 25th increased gradually over time (Fig. 1B). As Figure 1C shows, treatment intensification was observed in patients with undifferentiated arthritis along the time periods, whilst the intensity of treatment of patients fulfilling RA criteria was similar in the three subpopulations. In addition, we have observed a significant increase in the prescription of methotrexate from 73% to 85% of patients, whereas there was a significant decrease in the percentage of patients treated either with antimalarials or sulphasalazine (supplementary Table I). The use of leflunomide remain stable in about 35% of patients in all time periods. Gold salts and cyclosporine A, which were infrequently prescribed during the first years, are no longer used in recent years (supplementary Table I).

On the other hand, the percentage of patients that were prescribed BT during their first 2 years of follow-up significantly increased from 4.7% in the patients whose symptoms started between 2000 and 2004 to 12.8% for those included between 2010 and 2014 (p=0.045; Fig. 1D). In the intermediate group the percentage of patients receiving biologics was 7.2%.

Table III. Variables associated with the progression between baseline and two-year follow-up visits assessed in hands through Sharp score with the van der Heijde modification.

	Erosion component		Joint narrowing component	
	OR (95% CI)	p	OR (95% CI)	p
Age at disease onset (years)				
<45	Ref.	-	Ref.	-
45-65	2.81 (1.05 – 7.57)	0.040	1.75 (0.76 – 3.99)	0.186
>65	3.79 (1.36 – 10.57)	0.011	5.57 (2.42 – 12.86)	<0.001
Female gender	0.58 (0.28 – 1.18)	0.134	NI	NS
Rheumatoid factor	NI	NS	1.83 (0.92 – 3.64)	0.085
ACPA	NI	NS	0.54 (0.27 – 1.05)	0.071
Year of symptom onset				
2000-2004	Ref.	-	NI	NS
2005-2009	0.62 (0.31 – 1.26)	0.188	NI	NS
2010-2014	0.27 (0.09 – 0.78)	0.016	NI	NS
Cutpoints				
No/Low progression	1.27 (0.23 – 2.30)	-	1.41 (0.63 – 2.19)	-
Low/High progression	2.21 (1.14 – 3.28)	-	2.52 (1.69 – 3.35)	-

OR: odds ratio; CI: confidence interval; Ref: reference; NI: not included in the final model because not significant (NS); RF: rheumatoid factor; ACPA: anti-citrullinated proteins antibodies.

Disease activity during follow-up

Disease activity was significantly different between the 3 groups of patients, showing a trend to lower DAS28 score over time (Fig. 2A). As shown in Table 2 (left and mid sections), after adjustment by age at disease onset, gender, ACPA positivity and disease activity at baseline visit, patients included in PEARL during periods 2005-2009 and 2010–2014 had significantly lower disease activity than patients included at the earliest period. In addition, there was a non-significant trend to higher number of patients in remission at the end of follow-up in the patients included after 2004 than those included in the study between 2000 and 2004 (Fig. 2B), that reached statistical significance after adjustment by confounders (Table II, right section).

Radiological progression after 2-year follow-up

Although more than 50% of patients did not show an increase in the hand total SHS (Fig 3A), there was a significant trend to lower progression of the erosion score in the recent subpopulations (Fig 3B). No significant differences were observed in the progression of the narrowing score (Fig 3C). The multivariable analysis confirmed that after adjustment by gender and age, patients included in PEARL during the last period showed

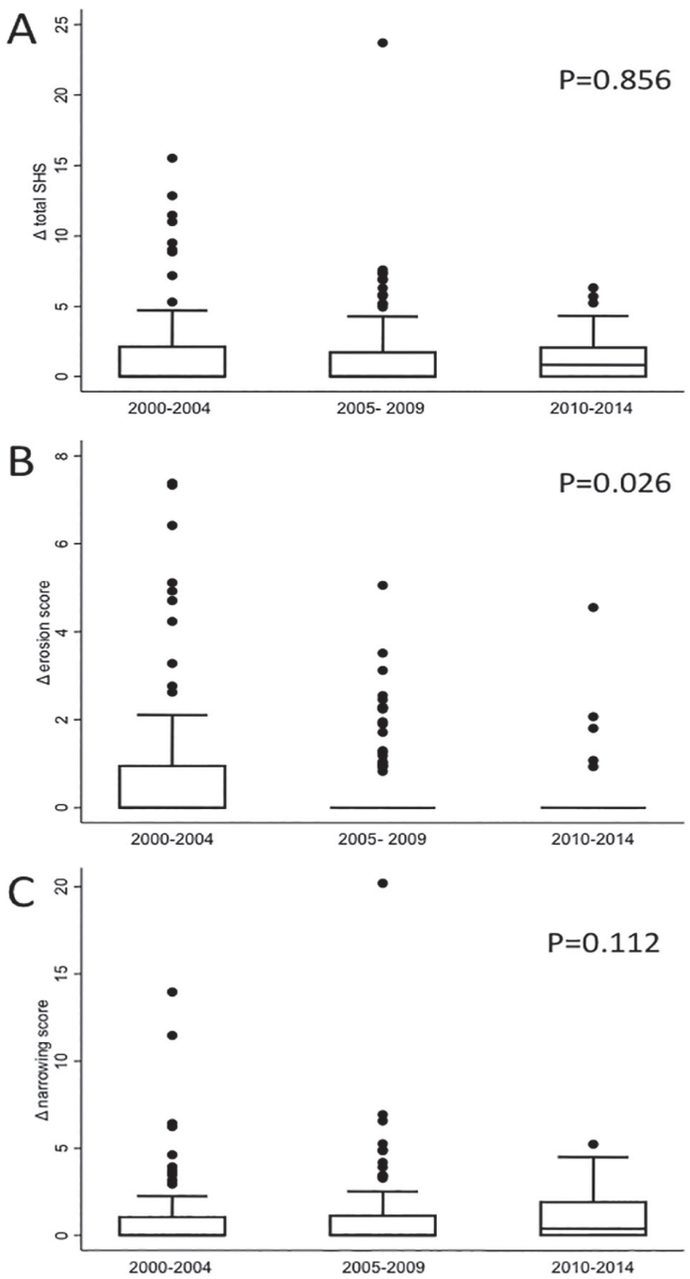

Fig. 3. Radiological progression in patients from the PEARL study depending on the year of symptoms onset.
A: Variation between baseline and 2-year follow-up visits in the Sharp score with the van der Heijde (SHS) modification assessed in hands;
B: Variation in the erosion component of the SHS;
C: Variation in the joint narrowing component of the SHS. Data are shown as median of the SHS or its components (line inside the box), as well as the percentiles 25,7 5 (lower and upper lines of the boxes, respectively), 10 and 90 (end points of the lines outside the boxes). Circles represent outliers.

significantly lower erosion score than those included between 2000 and 2004 (Table III, left section). Regarding joint space narrowing, only patients older than 65 years showed significantly higher progression than those younger than 45 years and this was the only variable significantly associated with this outcome (Table III, left section).

Discussion

The data shown in this article indicate that over the last 15 years rheumatologists in our department have progressively prescribed a more aggressive and earlier treatment to patients classified as undifferentiated arthritis. Those patient fulfilling RA criteria were intensively treated even since the early years of PEARL study, although the time to first DMARD have also decreased. The explanation for this finding is likely that we have accepted the concepts window of opportunity and treat-to-target believing that in this way our patients can reach better outcomes. In fact, the percentage of patients in remission and the radiological progression have improved in PEARL over these 15 years.

Due to the observational nature of our study we cannot determine how much have contributed each part of the strategy, intensification of treatment and earlier onset of DMARD, in the improvement of outcomes in PEARL. Furthermore, the way we calculate the variable IDT leads to an interaction between both factors, since starting earlier a DMARD has as a consequence a higher value of IDT. Nevertheless, our data provide information from real life supporting the usefulness of early and intense treatment with DMARD in patients with early arthritis.

The search for new severity biomarkers for RA is a challenge since, although large-scale GWAS have increased the genetic understanding of RA, the contribution of genes different to HLADRB1 is modest and in some cases it differs among ethnic groups (24). In addition, the data described in this work have an unexpected consequence to the research in severity biomarkers. Since our patients were treated earlier and in a more intense way over time, our availability of solid outcomes to detect new severity biomarkers is worse than 15-20 years ago. Radiographic progression had been considered the gold standard to analyse disease severity in RA until now (25). However, our capability to slow-down or even completely stop radiological progression has greatly improved during the last 15 years (26). In this regard, here we describe that almost no patient suffered radiological erosive progression since 2005. In addition, we have shown in PEARL that, in absence of a pre-established therapeutic protocol, ACPA-positive patients did not show more radiological progression than ACPA-negative patients and this observation was related to a more intense treatment in the ACPA-positive group (17).

Our study has a number of limitations, the most important being the fact that it describes the behaviour of rheumatologists in a tertiary hospital in Madrid and we do not know whether these findings can be extended to other hospitals in Spain or Europe. In addition, the way in which we calculate the intensity of DMARD treatment does not allow determining how each DMARD contributes to the improvement in outcomes. Finally, assessing only in hand x-rays may underestimate the radiological progression, since it has been described that evaluating only hand x-rays progression can be missed in 20–30% of cases (27), although we do not know whether these data can be extrapolated to the current management of early RA. In summary, our data reflect that DMARD treatment in patients with early arthritis during the first two years of evolution has been gradually intensified over the last 15 years. This approach has led to better outcomes but hampers the research to identify severity biomarkers. Therefore, it would be worthwhile developing a composite index to evaluate global severity in patients with early arthritis. This kind of tool, considering different aspects of the disease (radiological progression, treatment intensity, presence of systemic complications, disability, …) could help to develop a more efficient research on biomarkers for prediction of disease severity.

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