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Fatigue, older age, higher body mass index and female gender predict worse disability in early rheumatoid arthritis despite treatment to target: a comparison of two observational cohort studies from the United Kingdom

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ABSTRACT

Objectives:

Compare disease activity and disability over 2 years in early rheumatoid arthritis (RA) before and after implementation of treat to target (T2T) and identify predictors of adverse outcome.

Methods:

Yorkshire Early Arthritis Register (YEAR) recruited 725 patients with early RA between 2002-2009, treated with a step-up approach. The IACON study (Inflammatory Arthritis CONtinuum) recruited cases between 2010-2014 and treated to target. 384 IACON cases met 2010 ACR/EULAR criteria. Latent growth curves of change in 28 joint disease activity score (DAS28) and Health Assessment Questionnaire (HAQ) were compared between YEAR and IACON. Latent class growth analysis identified trajectories of change. Baseline predictors of trajectories were identified using logistic regression.

Results:

Mean DAS28 over 2 years was lower in IACON than YEAR. Latent trajectories of HAQ change in YEAR were: high stable (HS, 21% of cohort); moderate reducing (MR, 35%) and low reducing (LR, 44%). Only MR (66%) and LR (34%) were seen in IACON. In both cohorts, female gender and fatigue predicted adverse HAQ trajectories (HS and MR). Odds ratios (OR) for MR compared to LR for females were 2.58 (95% confidence interval 1.69, 4.49) in YEAR and 5.81 (2.44, 14.29) in IACON. OR per centimetre fatigue visual analogue score were 1.13 (1.07, 1.20) in YEAR and 1.16 (1.12-1.20) in IACON.

Conclusion:

T2T gave more favourable trajectories of change in DAS28 and HAQ, but adverse HAQ trajectory was more likely in females with greater fatigue, suggesting such patients would benefit from interventions to improve function as well as reduce inflammation.

SIGNIFICANCE AND INNOVATIONS

- Disability can persist despite suppression of inflammation in RA
- This phenomenon is more likely in females, older patients, those with greater body mass index and those with greater baseline fatigue

Disability is a well recognised adverse outcome in rheumatoid arthritis (RA), which impacts upon the health and wellbeing of individuals with the disease [1] and results in significant direct and indirect (that is, incurred due to time out of work) health care costs [2-4]. Modern RA management largely targets suppression of inflammation, a phenomenon undoubtedly related to substantial advances in pharmacological therapies over recent decades. In 2010, there was a step-change in RA management with the introduction of the treat to target (T2T) approach, which advocated frequent clinical review to achieve remission or low disease activity [5].

This approach is effective for reducing disease activity and achieving remission more rapidly [6, 7]. However, studies investigating the impact of T2T on functional outcome, measured by the Health Assessment Questionnaire (HAQ), have given different results. The open-label Computer Assisted Management in Early RA (CAMERA) study found no difference in the area-under the curve of HAQ over two years between groups treated to target and those receiving conventional step-up therapy [8]. Similarly, a randomized controlled trial from the British Rheumatoid Outcome Study Group (BROSG) compared aggressive RA therapy to symptomatic therapy, with HAQ as the primary outcome, and found that there was no significant difference in HAQ between the two treatment groups after 3 years [9]. Importantly, this study enrolled patients with established RA, whereas others have explored change in disability in early RA.

Greater improvement in HAQ was demonstrated in a T2T, compared to standard care group in the Dutch RA monitoring study (decrease in HAQ of 0.5, compared to 0.3 over 1 year), although HAQ was not the primary outcome investigated [10]. Similarly, reduction in HAQ after 12 months was greater in the French ‘GUEPARD’ study, where treatment was targeted at low disease activity (defined as disease

activity from counts of 28 joints, DAS28<3.2), compared to the French national observational cohort of early inflammatory arthritis 'ESPOIR' where cases received standard care. The median change in HAQ was -0.94 (95% confidence interval [CI]1.15 to -0.72) in GUEPARD compared to -0.68 (-0.81 to -0.55) in ESPOIR [11]. In the same study, DAS28 remission with no radiographic progression and HAQ<0.5 was more likely in the T2T group (32.3% of cases) than the standard care group (10.2%).

It is evident that management using T2T approaches improves DAS28 and achieves remission more rapidly, but it is not clear whether T2T has lead to equivalent advances in improving functional outcomes. Here, we compare the changes in DAS28 and HAQ over the first 2 years in early RA in two observational cohorts: the first, established in 2002, captured data on patients treated according to a traditional 'step-up' approach, whilst in the second cohort, initiated in 2009, patients were treated according to T2T. To our knowledge, this study is the first application of modern statistical techniques to evaluate the impact of T2T on functional outcome. We have used latent growth curve and latent class growth analyses (LCGA), in order to make use of all available DAS28 and HAQ records in our datasets. These methods are preferable to comparing 2 year change in DAS28 or HAQ, or average change over time, because fluctuations in disease activity and disability between the two time-points can be accounted for. Thus, a comprehensive assessment of change in disability was obtained and compared between the two cohorts.

PATIENTS AND METHODS

Data from patients recruited to Yorkshire Early Arthritis Register (YEAR, described previously [12]) between 2002-2009 were used. Briefly, YEAR recruited subjects aged over 18 with a consultant-made diagnosis of RA from 14 hospitals within Yorkshire, UK. They were enrolled within 24 months of RA symptom onset and followed for 2 years. Management was guided by a treatment protocol using a 'step-up' approach with synthetic disease modifying anti-rheumatic drugs (DMARD) and methotrexate (MTX) as the first line agent. Although deviations from the protocol occurred at the discretion of the treating rheumatologist, an initial dose of 7.5mg of MTX at the baseline assessment was suggested, escalating after 4 weeks to 10mg for 4 weeks, then 15mg for 4 weeks. Then it was increased to 20mg at the 3 month visit if disease was active at that point and the addition of Sulphasalazine (SSA) was recommended at 6 months if the response was inadequate. Active disease was judged by the treating physician and not specifically guided by composite measures of disease activity. After 9 months, the protocol recommended adding hydroxychloroquine or parenteral MTX. After 12 months, the protocol suggested switching to or adding Leflunomide. The treatment protocol is summarised in supplementary online Table 1. The Inflammatory Arthritis CONtinuum study (IACON) recruited cases aged over 18 with early inflammatory arthritis, at their first presentation to Leeds Teaching Hospitals NHS Trust, between 2010-2014. For the present study, IACON cases were selected if 2010 ACR/EUALR criteria for RA [13] were met at baseline or during follow up. There was no agreed treatment protocol; however, patients were treated in a single centre according to contemporary best practice in the UK, which included MTX as the first line DMARD. Treatment was rapidly escalated with the aim of achieving DAS28CRP remission (< 2.6). This included biologic DMARDs if indicated, in line with UK National Institute for Health

and Care Excellence guidelines [14]. Data were captured every 3 months for the first year of both studies and then every 6 months; however, clinical review with data capture occurred more often in IACON, according to the T2T regime (that is, if clinically indicated or remission not achieved). Written consent for inclusion into both studies was obtained from all participants. Ethical approval was granted for YEAR by the Northern and Yorkshire Research Ethics Committee (MREC/99/3/48) and by the Leeds (West) Research Ethics committee (09/H1307/98) for IACON.

For both studies, clinical data collected at baseline and each subsequent visit included: counts of swollen (SJC) and tender joints (TJC) from a total of 28, visual analogue scores (VAS, a 0 to 10 centimetre line where 0 represented no pain/fatigue and 10 represented worst pain/fatigue) and HAQ. Disease activity scores from counts of 28 joints (DAS28) were calculated from SJC, TJC and C-reactive protein (CRP). The body mass index (BMI) was obtained and patients were asked about tobacco smoking. Blood samples were used to determine CRP, baseline immunoglobulin M rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). ACPA were not routinely measured by hospital laboratories at the time of YEAR data collection, so were acquired retrospectively, using samples stored at minus 20℃ and laboratory methods described previously [15].

Statistical analysis

The cohorts were described using means and standard deviations for continuous normally distributed variables, median and interquartile range for non-normally distributed variables, and percentages for categorical data. As HAQ is an ordinal variable, it was transformed using Rasch analysis (discussed by Tennant and Conaghan [16]) to facilitate its use as an interval variable in statistical models.

Latent growth curve models described mean change in DAS28 and HAQ in YEAR and IACON and LCGA identified latent trajectories of change within the growth curves. Details of the Rasch transformation, latent growth curve models and LCGA are available as supplementary online data and supplementary online Tables 2-7. Multinomial logistic regression was used to identify baseline determinants of trajectory group. Analyses were carried out using Mplus version 6.1. Muthèn and Muthèn, Los Angeles, CA [17]. Missing data were handled using maximum likelihood estimation.

Three post-hoc analyses

There were fewer trajectories of change in HAQ in IACON than YEAR, with the loss of the most adverse (high stable) trajectory in IACON. We therefore investigated whether this result occurred simply because there were fewer IACON cases, by repeating the LCGA using all YEAR and IACON data in the same model. Then, to test whether cases from the T2T group were more likely to be classified in either trajectory, logistic regression was used in a model that included T2T as a predictor of trajectory class (together with interaction terms between T2T and all other independent variables to account for possible differences in effects of predictors on trajectory group between the two cohorts). We also tested whether the preferable outcome in IACON could have occurred because this group included patients not meeting RA criteria at baseline, by excluding these cases and repeating the LCGA. The final post-hoc analysis tested the effect of socio-economic status on trajectory membership in YEAR. This analysis used postal code (which was not available to the IACON study team) to derive the Index of Multiple Deprivation [18]. Results of the post-hoc analyses are given in online supplementary Tables 8-11.

RESULTS

Cohort characteristics

The analysis included 725 patients recruited to YEAR (traditional treatment) and 384 IACON (T2T) cases. Figure 1 illustrates how these numbers were derived. The 1987 ACR and 2010 ACR/EULAR RA classification criteria for RA were met in 77% and 95% YEAR cases, respectively. Of the IACON cases, 337 (88%) met either of the RA classification criteria at the baseline visit, the remainder met criteria at subsequent visits. 121 patients with early inflammatory arthritis were recruited to (currently unpublished) clinical trials rather than IACON. Of these, 47% entered trials with inclusion criteria of DAS28-ESR >3.2 at baseline and the remainder did not have disease activity-based inclusion criteria. The cohorts were similar with respect to the proportion of females, ACPA positive cases, cases who had ever smoked tobacco, mean age, BMI, fatigue VAS and HAQ at baseline. IACON included more cases with negative RF than YEAR which was possibly because YEAR cases were recruited if they had a consultant-made diagnosis and at the time of recruitment (2002-2009), ACPA were emerging as a clinical test. Therefore, RF could have been more important as an indicator of diagnosis for YEAR cases. Furthermore, baseline pain VAS and DAS28 were higher in YEAR. This was possibly because IACON captured all early inflammatory arthritis and therefore cases in IACON were recruited at an earlier stage of disease, which may have been when there was less inflammation. The difference in median symptom duration was not as large as expected (6.6 months in YEAR compared to 6.0 in IACON), but this could be because questions about symptom length were worded differently in the cohorts.

For IACON, the date of onset of symptoms most relevant to current complaint (judged by the physician) was used to calculate the symptom duration, or if unavailable, the patient reported symptom onset, then the date of onset of persistent swelling (for cases with prior palindromic RA). In YEAR, the patient was asked to recall when the symptoms began. Treatment differed between the two cohorts. At the 6 month visit, 70% of YEAR cases were taking MTX monotherapy and of these, 20% were taking 20mg per week and 6% were taking 25mg per week. Of the 34% of IACON cases taking MTX monotherapy at 6 months, 25% and 62% were taking 20 and 25mg MTX per week, respectively. MTX doses and DMARD use in YEAR and IACON are compared in online supplementary Figures S1 and S2, which illustrate that combination therapy with MTX and one other DMARD was used earlier and for a greater proportion of patients in IACON. Monotherapy with hydroxychloroquine was also more common in IACON patients, and this may be because IACON cases were at an earlier stage of RA, with less inflammation and therefore less aggressive therapy was indicated for these patients.

Mean change in DAS28 and HAQ over time in YEAR and IACON

Details growth curve models fit are provided in supplementary online Table 5. The latent growth curve models showed that mean DAS28 was lower throughout follow up in the T2T group (IACON) than the traditional therapy group (YEAR) and that a greater proportion of overall change in DAS28 occurred by 6 months in the T2T group: 0.86 of overall change (95% CI 0.71, 1.00) compared to 0.62 (0.34, 0.69). However, the difference in mean DAS28 between the two groups was less marked after 2 years, as shown in supplementary Figure S3. Although HAQ was initially

lower in IACON, the difference between mean HAQ in YEAR and IACON at 12 months was minimal, and mean HAQ was slightly higher in IACON at 2 years (Figure 2). The growth curve models represent mean change of the whole cohort and considerable variation between individuals is likely; therefore, distinct trajectories of change in DAS28 and HAQ were sought using LCGA.

Trajectories of change in DAS28 and HAQ

Details of fit of models with successive numbers of trajectories are provided in supplementary online Table 7. The fit of the growth curve model of change in DAS28 in IACON was not improved by adding trajectories. However, in YEAR, there were two trajectories of change in DAS28, as shown in Figure 3. These were interpreted to represent high stable and low reducing DAS28, based on the observed trends over time. There were 2 trajectories of change in HAQ in IACON (moderate reducing and low reducing) and 3 in YEAR (high stable, moderate reducing and low reducing), which are shown in Figure 4. The most disabled group, with HAQ of about 2 throughout follow-up, was described by the high stable trajectory; the low reducing HAQ trajectory was the most favorable, with lowest HAQ throughout follow-up and the moderate reducing trajectory described a group with average HAQ between these two.

Predictors of HAQ trajectory

Compared to low reducing trajectories, individuals were more likely to be classified into moderate reducing (YEAR and IACON) or high stable (YEAR only) trajectories if they were female, older, or had greater baseline fatigue (odds ratios [OR] are given in Table 2). Higher BMI was also statistically significantly associated with the high stable trajectory in YEAR and moderate reducing trajectory in IACON. The

association with BMI almost reached statistical significance for the moderate reducing trajectory in YEAR. Smoking (ever versus never) was associated with increased odds of the moderate reducing, compared to low reducing trajectory in YEAR, but was not a significant predictor in IACON. The effects of current and previous versus never smoking were tested separately, and again, smoking did not predict IACON HAQ trajectory, or high stable versus low reducing trajectories in YEAR. However, the significant effect of smoking on the moderate reducing trajectory described in Table 2 was present again, whereby past smokers were more likely than never-smokers to be classified in the moderate reducing compared to low reducing trajectory (OR 1.64, 95% CI 1.08, 2.51, p=0.022). Current smokers were not significantly more likely than never-smokers to be in the moderate reducing than the low reducing trajectory (OR 1.48, 95% confidence interval, CI, 0.94, 2.34, p=0.095).

DISCUSSION

In both cohorts, more favourable 'low reducing' trajectories of HAQ were identified, representing 44% and 34% of YEAR and IACON, respectively. The remainder of cases were classified by moderate reducing trajectories, and a high stable trajectory in YEAR. Although the absence of the high stable trajectory in IACON suggests a better outcome compared to YEAR, most (66%) IACON cases followed a moderate reducing trajectory in which mean HAQ score was 1.45 at baseline and 1.22 at 2 years, indicating ongoing disability for most of the cohort, despite treatment targeted at disease activity.

We considered whether there was no high stable trajectory in IACON because there were fewer cases in this group than in YEAR. In a post-hoc analysis whereby YEAR

and IACON data were analyzed together there were only 2 trajectories of HAQ (results available in supplementary online Table 8). Therefore, the two trajectory solution to the model of HAQ change in IACON was not due to the lower number of cases in IACON. We also considered whether the results could have arisen because IACON included 47 cases who did not meet RA criteria at the initial visit and conducted a further post-hoc analysis of the 337 cases meeting RA criteria at baseline. This gave similar results (shown in online supplementary Table 9), so the findings were not significantly affected by including cases who did not initially meet RA criteria. Furthermore, a comparison of trajectories of DAS28 between the two cohorts suggests an alternative explanation for the absence of the high stable HAQ trajectory in IACON. Two trajectories of change in DAS28 were identified in YEAR and 23% of cases followed a high stable trajectory with persistently elevated DAS28 of >4.5 (shown in Figure 3). However, there was no high stable DAS28 trajectory in IACON. Therefore, DAS28 over 2 years was more favorable for IACON than YEAR cases, consistent with previous evidence of improved control of disease activity with T2T. Lower disease activity over 2 years in IACON could explain a more favorable HAQ change in this group, that is, the absence of the high stable HAQ trajectory.

We investigated baseline predictors of adverse HAQ outcome and found that female gender, older age, higher BMI, and higher fatigue were associated with the high stable HAQ trajectory in YEAR and the moderate reducing trajectory in IACON. An association between female gender and adverse HAQ outcome has been noted before [19-23]. Similarly, morbid obesity has also been associated with worse HAQ [24] and it is possible that the inflammatory nature of adipose tissue contributes to inflammation in RA [25]. Fatigue is not often investigated as a predictor of functional outcome, but has been inversely associated with remission in RA [26]. This work

has supported previously noted associations of female gender and obesity with poor outcome and highlighted an under-reported association of baseline fatigue with adverse outcome. It was not possible to assess the effect of socio-economic status on outcome in IACON, because the data were not available to the study team. Therefore, this may be an unmeasured confounder and could have influenced the finding of an association of poor outcome with higher baseline BMI and fatigue. However, we obtained data on area-level social deprivation for YEAR, and a post-hoc analysis (results available in online supplementary Table 11) found that female gender, BMI, fatigue and social deprivation were all independent predictors of high stable, compared to low reducing HAQ trajectory in YEAR.

As this study used data from two early RA cohorts, in which standard care was provided within realistic clinical settings, the findings are relevant to routine clinical practice. An additional strength of the present analysis is the use of a Rasch transformed HAQ variable. Without this adjustment, HAQ is an ordinal measure, so change in either direction of a given number of units does not have the same meaning at the extremes of the scale as in the middle [27]. HAQ is often used as an interval variable in RA research, which is most problematic if changes in its value occur at the top or bottom of the scale.

The follow up duration for this study was 2 years, which may explain why the present analysis revealed only 2 trajectories of HAQ, compared to 4 in the Early RA Study (ERAS) and Norfolk Arthritis Register (NOAR) [19, 28], both of which used data from patients followed for substantially longer durations. The results presented here also differed from those of a previous report of trajectories of change in DAS28, where 3 trajectories over 12 months were identified [29]. One possible explanation is that the fit of our initial model was superior to the previously published work in which

trajectories of DAS28 were described within quadratic growth curve models. Quadratic models assume a quadratic (curve shaped) change over time, whereas freed loading growth curve models [30] were applied to the YEAR and IACON data, which allowed the growth curve to take any shape and resulted in very good fit of our data to the initial model. Fit of the growth curve models is described in online supplementary Table 6.

In summary, the findings from this work were consistent with the wealth of evidence supporting T2T approaches for the suppression of disease activity in early RA. Although there was some improvement in HAQ in the T2T group compared to the group treated with 'step-up' therapy, most cases followed a 'moderate' HAQ trajectory, in which there was significant functional impairment throughout follow-up. Women, older people, those with higher BMI, and those reporting greater fatigue at baseline were more likely to fall into this group, suggesting that such patients may benefit from therapies targeted at improving function in addition to those targeted at suppression of inflammation.

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TABLES

Table 1. Baseline clinical characteristics of YEAR and IACON

	YEAR (n=725)		IACON (n=384)	
Categorical variables	N (%)	Missing: N (%)	N (%)	Missing: N (%)
Female	485 (67)	0 (0)	267 (70)	0 (0)
RF positive (baseline)	465 (70)	57 (8)	217 (57)	33 (9)
ACPA positive	309 (64)	239 (33)	257 (67)	1 (0)
Ever smoked	433 (61)	17 (2)	233 (61)	16 (4)
Continuous variables				
Mean age (SD)	58 (14.1)	0 (0)	56 (14.8)	0 (0)
Median symptom duration in months (IQR)	6.6 (5.7)	0 (0)	6.0 (9.0)	0 (0)
Mean BMI (SD)	27.3 (6.0)	121 (17)	27.9 (5.6)	6 (2)
Mean fatigue VAS /cm (SD)	4.5 (2.6)	94 (13)	4.4 (2.9)	5 (1)
Mean pain VAS /cm (SD)	5.8 (2.6)	54 (7)	4.6 (2.8)	5 (1)
Mean DAS28 (SD)	4.7 (1.5)	102 (14)	3.94 (1.4)	18 (5)
Median SJC (IQR)	7 (4-12)	51 (7)	3 (1-7)	0 (0)
Median TJC (IQR)	9 (4-17)	53 (7)	6 (2-12)	0 (0)
Mean HAQ (SD)	1.27 (0.75)	47 (6)	1.12 (0.73)	9 (2)

ACPA, anti-citrullinated peptide antibodies; BMI, Body Mass Index; cm, centimetres; DAS28, disease activity score from counts of 28 joints; HAQ, Health Assessment Questionnaire; IACON Inflammatory Arthritis CONtinuum (T2T group); IQR, inter-quartile range; N, number (of cases); RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register (traditional treatment group).

Table 2. Predictors of high stable and moderate reducing HAQ trajectories in YEAR and IACON compared to low reducing trajectories

	High stable YEAR trajectory			Moderate reducing YEAR trajectory			Moderate reducing IACON trajectory		
Predictor Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age	1.04	(1.02,1.06)	<0.001	1.01	(0.99,1.02)	0.130	1.03	(1.01,1.05)	0.010
Female Gender	2.76	(1.69,4.49)	<0.001	1.80	(1.25,2.59)	0.002	1.87	(1.07,3.27)	0.027
BMI	1.08	(1.02,1.14)	0.006	1.04	(0.99,1.09)	0.065	1.12	(1.06,1.18)	<0.001
Smoking	1.55	(0.99,2.42)	0.055	1.57	(1.08,2.29)	0.018	0.91	(0.52,1.59)	0.747
ACPA positivity*	1.75	(0.99,3.08)	0.054	1.32	(0.84,2.08)	0.233	0.82	(0.47,1.45)	0.496
Fatigue VAS (cm)	1.25	(1.16,1.35)	<0.001	1.13	(1.07,1.20)	<0.001	1.05	(1.04,1.06)	<0.001
Symptom duration (months)	0.96	(0.91,1.01)	0.137	1.01	(0.97,1.05)	0.657	1.01	(0.99,1.02)	0.483

High stable trajectory (YEAR only): where HAQ remained highest (compared to other trajectory groups) and was 1.9-2.0 throughout follow-up. Moderate reducing trajectory (YEAR and IACON): HAQ was moderate throughout follow-up, but reduced from the baseline to remain mostly above 1 throughout. Low reducing trajectory: HAQ reduced from baseline and was then the lowest of the three trajectories throughout follow up and was approximately ≤0.25.

ACPA, anti-citrullinated peptide antibodies; BMI, Body Mass Index; CI, confidence intervals; cm, centimetres; IACON Inflammatory Arthritis CONtinuum (T2T group); OR, Odds Ratio; p statistical probability; VAS, visual analogue score; YEAR, Yorkshire Early Arthritis Register (traditional treatment group).

*Rheumatoid factor positivity was considered in separate models and the results did not change significantly.

Figure 1. Cases from YEAR and IACON cohorts included in analysis.

DAS28, disease activity score from counts of 28 joints; IACON, Inflammatory Arthritis Continuum; RA, rheumatoid arthritis; YEAR, Yorkshire Early Arthritis Register

Figure 2. Mean changes in HAQ in YEAR and IACON estimated by growth curve models.

Mean HAQ values estimated by the models at each time point are indicated on the chart

Figure 3. Trajectories of change in disease activity in YEAR.

Mean DAS28 values estimated by the models at each time point are indicated on the chart

Figure 4. Trajectories of change in HAQ in YEAR and IACON.