In patients with early inflammatory polyarthritis, ACPA positivity, younger age and inefficacy of the first non-biological DMARD are predictors for receiving biological therapy: results from the Norfolk Arthritis Register

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ABSTRACT

Objectives To identify baseline disease-related predictors in patients with early inflammatory polyarthritis (IP) for starting subsequent biological therapy and to determine if patients who failed their first non-biological disease-modifying antirheumatic drug (DMARD) within 6 months were more likely to need biological therapy.

Methods Patients with early IP recruited between 1990 and 1994 (cohort 1) and between 2000 and 2004 (cohort 2) in the Norfolk Arthritis Register were included in this study. The association between possible predictors with the start of biological therapy was assessed using Cox proportional hazards regression models.

Results 32/407 (7.9%) patients in cohort 1 and 45/416 (10.8%) patients in cohort 2 received biological therapy during follow-up. In both cohorts, anti-citrullinated protein antibody (ACPA) positivity (cohort 1, HR 7.62, 95% CI 2.46 to 23.58; cohort 2, HR 4.68, 95% CI 2.23 to 9.78) was the strongest predictor for starting biological therapy. In cohort 2, younger patients (HR 0.97, 95% CI 0.95 to 0.99) and patients who failed their first non-biological DMARD within 6 months due to inefficacy were also more likely to receive biological therapy (HR 2.35, 95% CI 1.05 to 5.27).

Conclusion Patients with early IP who are ACPA positive, are younger or who fail their first non-biological DMARD due to inefficacy within 6 months are more likely to need biological therapy.

The introduction of biological therapies has been an important therapeutic advance in the treatment of patients with rheumatoid arthritis (RA) making the achievement of sustained remission and retarded radiographic progression more feasible.[1–3] In the UK, based on recommendations by the National Institute for Health and Clinical Excellence (NICE), the use of biological therapies is restricted to patients with active RA, defined as a 28-joint disease activity score (DAS28) greater than 5.1 despite previous therapy with at least two disease-modifying antirheumatic drugs (DMARD), one of which should be methotrexate.[4 5]

It is important to be able to identify early in disease, patients who will need biological therapy later on, ie, have a worse disease course, so that they can be fast-tracked in the future to start biological therapies sooner. In one US retrospective cohort study, starting biological therapy was significantly associated with worse functional disability in the preceding 6 months, treatment with steroids and non-biological DMARD, younger age and lower income.[6] However, the mean disease duration at entry to the database was 16.2 years and information on disease activity early in the disease or genetic markers was not available in the study.

Using a primary-care based incidence register of patients with early inflammatory polyarthritis (IP), the objectives of this study were to identify baseline disease-related predictors in patients with early IP for starting biological therapy and to determine if patients who failed their first non-biological DMARD within 6 months of starting the first non-biological DMARD were more likely to need biological therapy later on.

PATIENTS AND METHODS

Clinical assessments and study population

Consecutive patients aged over 16 years with early IP from the Norfolk Arthritis Register (NOAR), recruited between 1990 and 1994 (cohort 1) or between 2000 and 2004 (cohort 2), were included in this study. Cohort 1 developed their IP in the prebiological era and cohort 2 in the biological era. Details of NOAR have been published previously.[7] Briefly, patients with swelling in two or more joints that lasted 4 weeks or longer were referred to NOAR. At baseline, patients were seen by a research nurse. Clinical assessments included the evaluation of the number of swollen and tender joints. The DAS28 based on three components including C-reactive protein ($DAS28(3)_{CRP}$) was calculated based on the 28 swollen and tender joint count and CRP value. Blood was collected to measure rheumatoid factor (RF; positive >40 UL), anti-citrullinated protein antibody (ACPA; ≥5 U/ml (Axis-Shield DIASTAT Kit; Axis-Shield, Dundee, Scotland)), CRP and for genetic analysis. Human leucocyte antigen genotyping was carried out as described previously and subtyping at the *HLA-DRB1* locus was performed to identify the presence of the shared epitope (SE).[8] In addition, patients completed the British version of the health assessment questionnaire (HA).[9] Clinical follow-up assessments were carried out annually for 3 years and then at 5, 7, 10, 12 and 15 years.

Patients with a symptom duration of 24 months or less at baseline, who had started a non-biological DMARD (except oral glucocorticoids) and had at

least 6 months follow-up after the start date, and with at least one total follow-up datum available were included in this study. Only patients who were non-biological DMARD and biological naive at symptom onset were included. We excluded patients who had participated in a clinical trial in whom the possible use of non-biological DMARD and biological therapies was therefore unknown (n=24). This study was approved by the Norwich Research Ethics Committee and all patients gave written informed consent.

Use of non-biological DMARD and biological therapies

The start and stop dates and reason for stopping non-biological DMARD and biological therapies was recorded at every visit. Based on information from medical notes or given by the patient, the reasons for stopping non-biological DMARD were defined as: (1) adverse reaction; (2) inefficacy; (3) disease remission; (4) planned course complete; (5) lack of compliance or (6) other. Non-biological DMARD failure within 6 months due to inefficacy was defined as: first non-biological DMARD stopped due inefficacy within 6 months and/or second non-biological DMARD added/started within 6 months of starting the first non-biological DMARD.

Statistical analysis

Data were analysed separately for cohorts 1 and 2. The association of baseline disease-related characteristics and the start of the first biological therapy was assessed using Cox proportional hazards regression models. HR (95% CI) were adjusted for age at symptom onset, gender and symptom duration at baseline. Variables with a p value less than 0.10 were then included in a multivariate Cox proportional hazards regression model to determine the independent contribution of each variable. The association with failure of the first non-biological DMARD due to inefficacy was analysed separately. For this analysis the survival time started 6 months after starting the first non-biological DMARD. For all models, patients were followed until the date of starting biological therapy or the last follow-up visit if no biological therapy was started. Subsequently, univariate regression analyses were restricted to patients who fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA cumulatively at any of the follow-up visits. All analyses were carried out using STATA release 10.

RESULTS

Patient characteristics

At baseline, the median symptom duration was 5 (3–10) months in cohort 1 and 7 (5–11) months in cohort 2; and 34% of cohort 1 and 65% of cohort 2 (previously) used non-biological DMARD and 7% and 31%, respectively, (previously) used oral glucocorticoids. The median follow-up duration since symptom onset was 180 (102–187) months in cohort 1 and 68 (61–89) months in cohort 2. The median time between symptom onset and start of the first non-biological DMARD was 9 (4–19) months in cohort 1 and 6 (4–12) months in cohort 2. Fifteen (3.7%) patients in cohort 1 and 36 (8.7%) patients in cohort 2 stopped taking the first non-biological DMARD within 6 months due to inefficacy.

The use of biological therapy

Thirty-two (7.9%) patients in cohort 1 and 45 (10.8%) patients in cohort 2 started biological therapy after a median time since symptom onset of 143 (118–159) and 47 (24–69) months, respectively (table 1). The median age at symptom onset of patients who subsequently used biological therapy was 47 (35–55) years in cohort 1 and 50 (41–55) years in cohort 2 compared with, respectively, 54 (44–65) years in cohort 1 and 58 (48–70) years in cohort 2 in those who did not use biological therapy (table 2). Eighty-one per cent (cohort 1) and 70.3% (cohort 2) who used biological therapy were ACPA positive at baseline compared with 42.3% (cohort 1) and 36.2% (cohort 2) in those who did not use biological therapy; 33.3% (cohort 1) and 22.0%

Table 1 Baseline characteristics cohort 1 and cohort 2

	N	Cohort 1 (n=407)	N	Cohort 2 (n=416)
Age at symptom onset (years)	407	53 (43–64)	416	57 (48–69)
Gender (female)	407	250 (61%)	416	269 (65%)
Baseline visit				
Symptom duration (months)	407	5.4 (3.0–10.0)	416	6.7 (4.5–11.4)
RA (1987 ACR criteria)	407	255 (62.7%)	416	220 (52.9%)
No of swollen joints	407	7 (3–14)	416	3 (1–7)
No of tender joints	407	7 (2–14)	416	3 (0–8)
CRP (mg/L)	336	10 (2–27)	363	12 (4–26)
$DAS28(3)_{CRP}$	336	4.5 (3.5–5.5)	363	3.7 (2.8–4.7)
HAQ score	398	1.0 (0.5–1.6)	408	1.0 (0.5–1.8)
RF (positive)	368	160 (43.5%)	371	155 (41.8%)
ACPA (positive)	288	130 (45.1%)	341	136 (39.9%)
SE (no of alleles)				
0	351	115 (32.8%)	371	135 (36.4%)
1		170 (48.4%)		178 (48.0%)
2		66 (18.8%)		58 (15.6%)
Previous or current DMARD use	407	142 (34%)	416	269 (65%)
Previous or current steroid use	407	29 (7%)	416	130 (31%)
Smoking				
Never smoked	407	129 (31.7%)	377	113 (30.0%)
Ex-smoker		162 (39.8%)		166 (44.0%)
Current smoker		116 (28.5%)		98 (26.0%)

Patients in cohort 1 were recruited between 1990 and 1994 and patients in cohort 2 were recruited between 2000 and 2004. Values are median (IQR) for continuous variables and numbers (%) for categorical variables.
ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; CRP, C-reactive protein; $DAS28(3)_{CRP}$, 28-joint disease activity score based on three components including CRP; DMARD, disease-modifying antirheumatic drug; HAQ, health assessment questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor; SE, shared epitope.

Table 2 Baseline characteristics and follow-up data on non-biological DMARD use of biological therapy-naive patients and patients who started to use biological therapy

	Cohort 1		Cohort 2	
	Biological therapy-naive group (n=375)	Biological therapy group (n=32)	Biological therapy-naive group (n=371)	Biological therapy group (n=45)
Age at symptom onset (years)	54 (44–65)	47 (35–55)	58 (48–70)	50 (41–55)
Gender (female)	224 (60%)	26 (81%)	232 (63%)	37 (82%)
Baseline characteristics				
Symptom duration (months)	5.4 (3.0–9.7)	5.4 (3.3–12.9)	6.7 (4.4–11.7)	6.4 (4.6–8.7)
RA (1987 ACR criteria)	230 (61.3%)	25 (78.1%)	194 (52.3%)	26 (57.8%)
No of swollen joints	8 (2–14)	5 (3–12)	3 (1–7)	4 (1–7)
No of tender joints	7 (2–14)	5 (2–10)	3 (0–8)	5 (1–8)
CRP (mg/L)	10 (2–27)	10 (4–23)	12 (4–25)	16 (3–36)
$DAS28(3)_{CRP}$	4.5 (3.5–5.5)	4.3 (3.2–5.4)	3.7 (2.8–4.6)	4.4 (3.0–5.0)
HAQ score	1 (0.5–1.6)	1.1 (0.5–1.5)	1.0 (0.5–1.6)	1.1 (0.4–1.9)
RF (positive)	142 (42.0%)	18 (60.0%)	139 (41.5%)	16 (44.4%)
ACPA (positive)	113 (42.3%)	17 (81.0%)	110 (36.2%)	26 (70.3%)
SE				
0 allele	108 (33.6%)	7 (23.3%)	127 (38.5%)	8 (19.5%)
1 allele	157 (48.9%)	13 (43.3%)	154 (46.7%)	24 (58.5%)
2 alleles`	56 (17.5%)	10 (33.3%)	49 (14.9%)	9 (22.0%)
Smoking				
Never smoked	116 (30.9%)	13 (40.6%)	104 (31.3%)	9 (20.0%)
Ex-smoker	153 (40.8%)	9 (28.1%)	149 (44.9%)	17 (37.8%)
Current smoker	106 (28.3%)	10 (31.3%)	79 (23.8%)	19 (42.2%)
Follow-up data				
Follow-up duration (months)	168 (96–186)	188 (182–193)	68 (60–88)	70 (64–91)
Time until starting first DMARD since symptom onset (months)	9 (4–19)	10 (5–16)	6 (4–12)	7 (4–8)
Time until starting first biological therapy since symptom onset (months)		143 (118–159)		47 (24–69)
First prescribed biological therapy				
Etanercept		11 (34%)		12 (27%)
Infliximab		14 (44%)		10 (22%)
Adalimumab		6 (19%)		23 (51%)
Rituximab		1 (3%)		0
No of non-biological DMARD before start first biological therapy		3.3 (1.4)		3.0 (1.3)
Used steroids before starting biological agent (yes)		21 (66%)		23 (51%)

Patients in cohort 1 were recruited between 1990 and 1994 and patients in cohort 2 were recruited between 2000 and 2004. Values are median (IQR) or mean (SD) for continuous variables and numbers (%) for categorical variables.
ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; CRP, C-reactive protein; $DAS28(3)_{CRP}$, 28-joint disease activity score based on three components including CRP; DMARD, disease-modifying antirheumatic drug; HAQ, health assessment questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor; SE, shared epitope.

(cohort 2) of biological therapy users versus 17.5% (cohort 1) and 14.9% (cohort 2) of biological therapy non-users carried two SE alleles.

Infliximab was the most common first biological therapy in cohort 1 (44%), whereas in cohort 2 this was adalimumab (51%). On average, patients in cohort 1 used 3.3 (SD 1.4) and patients in cohort 2 used 3.0 (SD 1.3) non-biological DMARD before receiving biological therapy.

Predictors for starting biological therapy

In both cohorts, ACPA positivity was the strongest predictor for starting biological therapy (cohort 1, HR 7.62, 95% CI 2.46 to 23.58; cohort 2, HR 4.66, 95% CI 2.23 to 9.78) (table 3). Compared with the carriage of no alleles, those with two copies of SE were more likely to start biological therapy (cohort 1, HR 3.07, 95% CI 1.15 to 8.17; cohort 2, HR 3.25, 95% CI 1.25 to 8.47). However, in cohort 2, the association between homozygosity for the SE versus carrying one or no SE alleles was no longer significant. Younger patients were more likely to receive biological therapy in cohort 2 (HR 0.97, 95% CI 0.95 to 0.99). A similar association was seen in cohort 1, but this did not reach statistical significance. There was a non-significant trend towards an association between female gender and the start of biological therapy in both cohorts. RF positivity and a diagnosis of satisfying the 1987 ACR criteria for RA were both associated with the start of biological therapy in cohort 1, but not in cohort 2. In cohort 2, current smokers compared with non-smokers, but not ex-smokers, were more likely to start biological therapy. Neither functional disability nor $DAS28(3)_{CRP}$ measured at baseline was associated with the start of biological therapy. However, in cohort 2 the number of swollen joints was associated with starting biological therapy (HR 1.06, 95% CI 1.00 to 1.12) as was failing the first non-biological DMARD within 6 months due to inefficacy (HR 2.35, 95% CI 1.05 to 5.27); associations not observed in cohort 1.

In multivariate regression analysis ACPA positivity (HR 6.68, 95% CI 1.75 to 25.41), fulfilment of ACR 1987 criteria (HR 4.15, 95% CI 1.14 to 15.02) and younger age (HR 0.96, 95% CI 0.92 to 1.00) were significant independent predictors for starting biological therapy in cohort 1. In cohort 2, the significant independent predictors were ACPA positivity (HR 4.19, 95% CI 1.75 to 10.02), younger age (HR, 0.94, 95% CI 0.92 to 0.97) and higher number of swollen joints (HR 1.11, 95% CI 1.02 to 1.22).

When restricting the univariate analyses to patients who fulfilled the 1987 ACR criteria for RA cumulatively during follow-up (n=378 in cohort 1 and n=340 in cohort 2), ACPA positivity remained the strongest predictor in both cohorts (table 3). In cohort 2, the number of swollen joints measured at baseline and failing the first DMARD due to inefficacy were no longer predictors for starting biological therapy. The significant association

Table 3 Predictors for starting biological therapy in respectively the first and second cohort

	Cohort 1 (1990–4)		Cohort 2 (2000–4)	
	Total study population (n=407)	RA population (n=378)	Total study population (n=416)	RA population (n=340)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age at symptom onset	0.98 (0.96 to 1.01)	0.98 (0.95 to 1.00)	0.97 (0.95 to 0.99)	0.96 (0.94 to 0.98)
Female gender	2.23 (0.91 to 5.47)	2.15 (0.87 to 5.27)	2.09 (0.97 to 4.51)	1.76 (0.81 to 3.81)
Baseline variables:				
Symptom duration (per month)	1.04 (0.98 to 1.11)	1.04 (0.98 to 1.11)	0.97 (0.91 to 1.02)	0.96 (0.91 to 1.02)
RA (1987 criteria)	2.52 (1.08 to 5.91)	2.02 (0.87 to 4.72)	1.51 (0.82 to 2.79)	0.99 (0.53 to 1.82)
No of swollen joints	1.00 (0.94 to 1.05)	0.98 (0.93 to 1.04)	1.06 (1.00 to 1.12)	1.04 (0.98 to 1.09)
No of tender joints	0.97 (0.92 to 1.02)	0.97 (0.92 to 1.02)	1.02 (0.98 to 1.06)	1.01 (0.97 to 1.06)
CRP (mg/L)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)
$DAS28(3)_{CRP}$	1.05 (0.79 to 1.41)	1.00 (0.74 to 1.33)	1.28 (0.99 to 1.66)	1.17 (0.90 to 1.52)
HAQ score	1.15 (0.68 to 1.96)	1.08 (0.64 to 1.84)	1.45 (0.95 to 2.21)	1.35 (0.88 to 2.07)
Positive RF	2.78 (1.31 to 5.90)	2.62 (1.24 to 5.54)	1.32 (0.68 to 2.58)	1.09 (0.56 to 2.16)
Positive ACPA status	7.62 (2.46 to 23.58)	6.63 (2.17 to 20.22)	4.68 (2.23 to 9.78)	3.74 (1.76 to 7.92)
Shared epitope, no of alleles				
0	1	1	1	1
1	1.32 (0.52 to 3.34)	1.22 (0.49 to 3.07)	2.44 (1.09 to 5.46)	2.15 (0.96 to 4.79)
2	3.07 (1.15 to 8.17)	2.92 (1.10 to 7.76)	3.25 (1.25 to 8.47)	2.60 (1.00 to 6.77)
Smoking status				
Non-smoker	1	1	1	1
Ex-smoker	0.75 (0.32 to 1.79)	0.78 (0.33 to 1.85)	1.88 (0.83 to 4.22)	2.16 (0.96 to 4.90)
Current smoker	1.14 (0.49 to 2.63)	1.28 (0.55 to 1.85)	3.71 (1.66 to 8.30)	3.74 (1.66 to 8.41)
Treatment effect				
DMARD failure due to inefficacy*	0.83 (0.11 to 6.10)	0.80 (0.11 to 5.86)	2.35 (1.05 to 5.27)	2.16 (0.96 to 4.85)

Patients in cohort 1 were recruited between 1990 and 1994 and patients in cohort 2 were recruited between 2000 and 2004. HR (95% CI) age at symptom onset adjusted for gender and symptom duration; HR (95% CI) gender adjusted for age at symptom onset and symptom duration; HR (95% CI) symptom duration adjusted for age at symptom onset and gender; all other baseline variables adjusted for age at symptom onset, gender and symptom duration.
*Unadjusted HR (95% CI).
ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; $DAS28(3)_{CRP}$, 28-joint disease activity score based on three components including CRP; DMARD, disease-modifying antirheumatic drug; HAQ, health assessment questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor.

of two copies of SE and failing the first non-biological DMARD with starting biological therapy previously observed in cohort 2 did not quite reach statistical significance in the RA population (respectively, p=0.062 and p=0.051).

DISCUSSION

In this primary care-based inception cohort of patients with recent-onset IP who used at least one non-biological DMARD during follow-up, 7.9% of patients who were registered in the prebiological therapy era (cohort 1) and 10.8% of patients who were registered in the biological therapy era (cohort 2) received biological therapies within a median of 11.2 and 3.9 years from symptom onset, respectively. For patients in cohort 1, biological therapies only became available 5–10 years after registration in the NOAR cohort. Registration into cohort 2 started at approximately the same time as biological therapies became available in the UK. It, therefore, seems appropriate to show the results of these two cohorts separately.

A positive ACPA, measured at baseline, was the strongest predictor for starting biological therapy in both cohorts. The ACPA status was not known to the physician at the time treatment was started, and so cannot have directly influenced treatment decisions. Previous studies have shown that ACPA is a marker of disease severity[10] and is strongly associated with joint damage,[11–14] independent of RF status. The genetic contribution of SE to RA susceptibility[15 16] and the production of ACPA[17–19] is well established. The linkage between SE and disease progression has, however, been investigated less.[20–22] In univariate analysis, but not multivariate regression analysis, we found in both cohorts that, compared with the carriage of no alleles of SE, carriers of two copies of SE were more likely to start biological therapy. Interestingly, we did not find an association between $DAS28(3)_{CRP}$ or functional disability at baseline, factors often associated with a worse disease course, with the need to start biological therapy. We did not look at the cumulative disease activity, which may be an independent predictor for starting biological therapy.

Patients in cohort 2 who failed their first non-biological DMARD in the first 6 months due to inefficacy were more likely to receive biological therapy. This association is probably not observed in cohort 1 because biological therapy was not available until later in the disease. In a previous study from NOAR, we found that patients who discontinued their first treatment within 6 months experienced more deterioration in physical functioning in the long term.[23] Given these findings, it may be appropriate to fast-track these patients for biological therapy as soon as they have failed their first non-biological DMARD for inefficacy.

Only one other study has looked at predictors of starting biological therapy. In the US ARAMIS database high levels of functional disability were associated with the initiation of biological therapy.[6] In both the US study and our study, biological therapies were more often prescribed to younger patients. In general, there seems to be a trend towards less prescribing of non-biological DMARD and biological therapies in older patients,[24 25] despite the fact that there is no difference in efficacy or tolerability of more aggressive treatment strategies in patients aged under 65 years than in those aged 65 years or older.[26]

This study comprised patients with IP recruited to a primary care-based inception cohort. Some people may argue that the disease course and applied treatment strategies may differ between patients with IP and RA and that biological therapy may only be prescribed to patients with RA. In our study population, 76/77 (98.7%) patients using biological therapy fulfilled the criteria for

RA at some point during follow-up. However, some of these patients were not classified as having RA at baseline (33%), and when trying to identify predictors for the need to start biological therapy in patients with recent onset arthritis it is important to include all patients with IP in the analysis.

Overall, the factors identified in this study as predictors for receiving (or deciding to prescribe) biological therapy are a combination of factors associated with severe disease progression such as ACPA positivity, SE status, failure on the first non-biological DMARD and current smoking, plus demographic characteristics of the patients such as age and gender. Interestingly, none of these factors is included in the National Institute for Health and Clinical Excellence guidance for prescribing biological therapies in RA.

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Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Norwich Research Ethics Committee UK.

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