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Time to first treatment is associated with a refractory course of rheumatoid arthritis

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Background

It is an ongoing matter of research, whether the natural course of rheumatoid arthritis (RA) can be altered by an early intervention, a concept historically referred to as the "window of opportunity".[1-3] So far, only short-term disease activity outcomes have been investigated (e.g. "remission off drugs"), which are, however, inherently affected by the unknown rate of underlying rate of self-limiting disease. It is unclear, whether among those, who really develop RA, the disease course is really affected by the timing of their initial treatment.

Objective

To explore whether the long-term course of RA is different according to the delay of initial treatment.

Patients and Methods

Patients were identified from a longitudinal clinical database, and patients with refractory RA ("reRA") were compared with patients with treatment amenable RA ("taRA"). ReRA was defined as ≥3 treatment courses (≥1 biological) over ≥18 months since diagnosis without reaching low disease activity (LDA) or remission (REM) defined by a Clinical Disease Activity Index (CDAI, ≥10); taRA patients reached at least LDA within their first 2 treatment courses. We performed both matched and adjusted logistic regression analysis to compare differences in timing of first treatment between these two groups.

Refractory RA (reRA)
- Moderate/High disease activity
- ≥ 3 treatment courses
- ≥ 1 biological treatment
- Disease duration ≥ 18 months

Therapeutically amenable RA (taRA)
- Remission/low disease activity
- ≤ 2 treatment courses
- Disease duration ≥ 18 months

Results

We enrolled 412 patients, of whom 70 were reRA and 102 taRA; 240 patients fulfilled neither definition. As shown in table 1, reRA patients were more frequently female (92.9 vs. 70.6%, p<0.001), younger (44.37 vs. 51.14 years, p=0.002), and had higher CDAI levels at first presentation (26.06 vs. 15.39, p<0.001); time to first DMARD treatment was significantly longer for reRA than taRA (3.17 vs. 1.45 years, p=0.001).
In the multivariate model of all 412 patients, these differences were significant for treatment delay (p=0.007), female gender (p=0.026) and disease activity (p=0.001); after matching reRA with taRA patients for the time point of their initial presentation at our clinic, treatment delay was significantly longer when tested univariately (p=0.013) as well as after adjustment for other significant predictors (p=0.027, table 2).
We then developed a matrix model based on this analysis with predicted probabilities of developing reRA (figure 1).

Features	Population					Differences (p-value)		
Characteristics	reRA (n=70)	Other (n=240)	taRA (n=102)	reRA matched** (n=50)	taRA matched** (n=50)	Across all three groups	reRA vs taRA (unmatched)	reRA vs taRA (matched**)
Female (%)	92.9	75.4	70.6	94.0	70.0	**0.002**	**<0.001**	**0.002**
Symptom Onset (month/year)	03/2002 (09/1993; 01/2006)	02/2003 (12/1995; 11/2008)	07/2007 (11/2002; 02/2011)	02/2004 (01/1997; 10/2007	12/2006 (10/2000; 11/2009	**<0.001**	**<0.001**	0.064
Age at Symptom Onset (years)	44.37 (14.44)	46.88 (14.53)	51.14 (14.08)	46.73 (14.02)	53.42 (12.11)	**0.006**	**0.002**	**0.012**
First Visit (month/year)	12/2005 (03/2002; 03/2009)	06/2006 (08/2001; 08/2010)	12/2009 (10/2005; 11/2012)	06/2007 (12/2003; 07/2010	07/2007 09/2004; 08/2010)	**<0.001**	**<0.001**	0.786
Time to First Treatment (years)	3.17 (4.10)	1.38 (2.61)	1.45 (2.80)	2.61 (3.76)	0.88 (0.97)	**<0.001**	**0.001**	**0.003**
RF pos. (%)	58.6	57.7	62.7	56.0	58.0	0.687	0.581	0.840
ACPA pos. (%)	61.4	60.3	63.7	62.0	62.0	0.833	0.759	1
CRP (mg/dL)	2.12 (2.41)	2.10 (2.41)	2.27 (3.67)	2.20 (2.57)	2.92 (4.77)	0.781	0.775	0.361
ESR (mm/h)	41.09 (27.35)	33.04 (25.32)	38.49 (30.21)	40.92 (26.83)	38.87 (30.16)	0.080	0.609	0.752
HAQ (0-3)	1.219 (0.975)	0.792 (0.700)	0.762 (0.736)	1.257 (0.948)	0.859 (0.693)	**0.001**	**0.003**	**0.044**
PGA (0-100)	58.65 (24.25)	43.03 (25.25)	43.11 (23.62)	60.16 (25.75)	45.51 (18.77)	**<0.001**	**<0.001**	**0.003**
EGA (0-100)	39.22 (20.42)	31.72 (21.29)	24.25 (18.94)	37.67 (21.38)	26.16 (19.46)	**<0.001**	**<0.001**	**0.009**
TJC 28 (0-28)	9.81 (7.06)	5.42 (6.54)	4.18 (4.76)	8.90 (6.73)	5.36 (5.34)	**<0.001**	**<0.001**	**0.005**
SJC 28 (0-28)	6.35 (5.66)	5.07 (4.74)	4.30 (4.42)	6.00 (4.98)	4.30 (4.63)	**0.026**	**0.009**	0.083
CDAI (0-76)	26.06 (12.22)	17.94 (12.49)	15.39 (9.81)	25.36 (11.98)	16.93 (9.42)	**<0.001**	**<0.001**	**<0.001**
SDAI (CDAI+CRP)	28.26 (13.28)	21.09 (18.90)	18.08 (11.88)	27.63 (12.66)	20.39 (12.57)	**0.001**	**<0.001**	**0.009**
First X-ray (0-440)	37.78 (50.16)	36.11 (58.88)	25.68 (57.76)	25.64 (36.05)	26.56 (59.22)	0.359	0.198	0.843
Current CDAI (0-76)	20.58 (10.13)	6.80 (7.90)	3.08 (2.76)	20.93 (10.03)	3.07 (2.90)	**<0.001**	**<0.001**	**<0.001**
Current SDAI (CDAI+CRP)	22.39 (10.54)	6.96 (7.50)	3.41 (2.84)	23.06 (10.27)	3.53 (3.18)	**<0.001**	**<0.001**	**<0.001**

Table 1. Patient characteristics at first clinical visit. Date (median, quartiles) / Mean (SD) / %, as applicable
* ANOVA or Chi², as appropriate; ** matched for date of first clinical visit

Characteristics	Cohort study: reRA n=70, non-ReRA n=342				Case / control study: reRA n=50, taRA n=50*			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	Sig. (p)	OR (95% CI)	Sig. (p)	OR (95% CI)	Sig. (p)	OR (95% CI)	Sig. (p)
Time to First Treatment	1.15 (1.07; 1.24)	**<0.001**	1.12 (1.03; 1.21)	**0.007**	1.63 (1.11; 2.38)	**0.013**	1.75 (1.07; 2.87)	**0.027**
Female gender	4.57 (1.78; 11.72)	**0.002**	3.07 (1.14; 8.23)	**0.026**	6.71 (1.80; 25.00)	**0.005**	6.92 (1.43; 33.56)	**0.016**
Age at Symptom Onset	0.98 (0.97; 1.00)	**0.048**	0.99 (0.96; 1.01)	0.181	0.96 (0.93; 0.99)	**0.015**	0.97 (0.93; 1.01)	0.093
CDAI	1.06 (1.03; 1.08)	**<0.001**	1.06 (1.03; 1.08)	**0.001**	1.08 (1.03; 1.14)	**0.001**	1.09 (1.03; 1.15)	**0.002**

Table 2. Main analysis comparing reRA vs taRA in a case control study (adjusted logistic regression model) and reRA vs non-reRA in a cohort study (logistic regression model)
* matched for date of first clinical visit

Conclusion

Our data suggest that delay to initial treatment affects the long-term course of RA. Earlier treatment initiation thus may change the severity of RA.

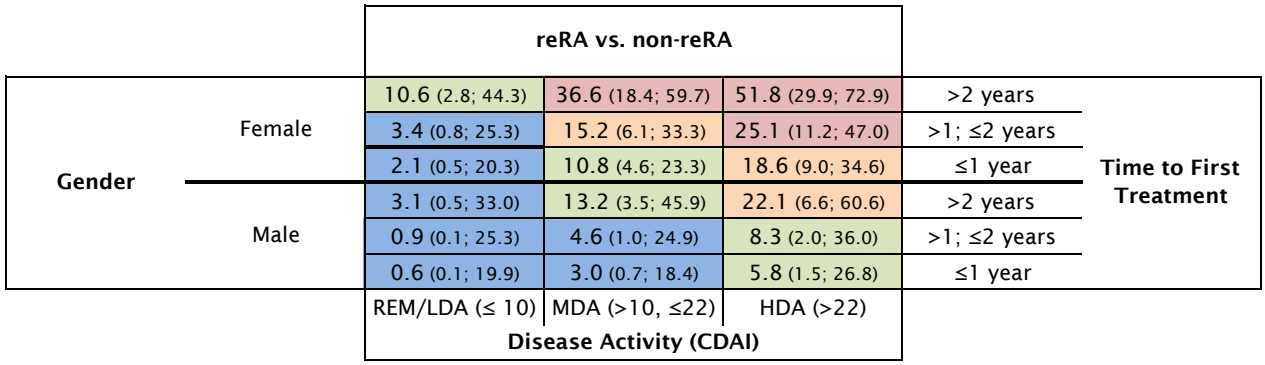

Figure 1. Matrix risk model for the probability (95% CI) of reRA including all selected baseline risk factors estimated for the first clinical visit in 2010.

References

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