Risk factors for Stroke in Patients with Rheumatoid Arthritis – Results from the German Biologics Register

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RABBIT

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Background & Objectives

Patients with rheumatoid arthritis (RA) are at increased risk of stroke. This event is associated with considerable sequelae and may result in death or major physical and neurological disability. Despite its clinical relevance, data regarding stroke are rare. Our objective was to analyse the impact of different risk factors on the development of stroke within our German biologics register RABBIT.

Patients & Methods

RABBIT is an ongoing prospective cohort study. Since 2001 patients have been enrolled at start of an approved biological therapy or a new synthetic DMARD treatment after at least one DMARD failure (nbDMARD group).

During follow-up rheumatologists assess regularly (at baseline, after 3 and 6 months and thereafter every 6 months) the clinical status and adverse events according to the ICH guidelines as well as treatment details.

All patients enrolled in the register until 31.08.2012 with at least 3 months of follow-up were included in this analysis. All reports of stroke were included, transient ischemic attacks (n=26) were not. Diagnoses of stroke were re-validated at on-site visits with examinations of medical records as well as hospital reports.

To assess the impact of different risk factors for stroke we performed a multivariate Cox regression analysis. Patients treated with biologics were considered to be exposed to these drugs up to 6 (rituximab: 12) months after the last dose.

	nbDMARDs	TNF Inhibitors	Other biologics
N	3405	5293	1499
Age	57.5 (12.2)	54.9 (12.5)	57.5 (12.5)
Women	76.7 %	76.7 %	78 %
Years of disease duration	7.9 (8.3)	11.3 (9.4)	12.3 (9.6)
Previous bDMARDs	0 (0.2)	0.2 (0.6)	1.3 (1.1)
Previous nbDMARDs	1.6 (0.9)	3 (1.3)	2.6 (1.1)
DAS28	4.8 (1.3)	5.5 (1.3)	5.4 (1.3)
Physical function [% of 100]	69.4 %	60.5 %	57.9 %
Heart failure	0.9 %	2.2 %	4.3 %
Coronary artery disease	5.4 %	5.4 %	7.5 %
Hypertension	36.5 %	35.6 %	40.9 %
Atrial fibrillation	0.3 %	0.6 %	0.6 %
Smoking (ever)	42.4 %	38.5 %	42.9 %
Time of follow up in months	39.7 (30.1)	41.7 (29.2)	31 (19.5)

Tab 1. Patient characteristics at baseline. Where not otherwise indicated the values represent mean (SD).

Results

Of 10,197 patients included, 114 experienced a stroke.

As relevant comorbidities we investigated diabetes, coronary heart disease, heart failure, hypertension and atrial fibrillation. In a univariate model all these differences were significantly associated, however in the multivariate model only hypertension and atrial fibrillation achieved statistical significance.

Other significant risk factors for the development of stroke were older age, disease activity (measured with the DAS28(ESR)) and smoking (Table 2). Not significantly associated were functional capacity and treatment with TNF inhibitors or other biologics and the use of glucocorticoids. DAS28 was a better predictor than erythrocyte sedimentation rate alone.

	HR (multivariate)	P-value	HR (univariate)	P-value
Male sex	1.46	0.08	1.58	0.02
Treatment with TNF Inhibitors	0.98	0.91	0.82	0.29
Treatment with other biologics	0.94	0.79	1.07	0.79
DAS28 (per unit)	1.52	<0.01	1.64	<0.01
Smoking (ever)	1.53	0.04	1.44	0.07
Age (by 10 years)	1.59	<0.01	1.86	<0.01
Hypertension	1.71	<0.01	2.79	<0.01
Atrial fibrillation	3.51	0.01	4.92	<0.01
Coronary heart disease	1.31	0.39	3.14	<0.01
Diabetes	1.19	0.40	2.02	0.01
Heart failure	1.01	0.97	3.37	0.01

Tab 2. Results of the multivariate Cox regression model. Disease activity was included in the model as time-varying variable (changes were considered).

High disease activity and co-morbid conditions were significantly associated with the development of a stroke. Treatment with biologics was not associated with this risk in an "as treated" approach which applies a 6-month risk window of the RA treatment prior to the event. The results were consistent in a sensitivity analysis of different approaches.

All patients of the dataset were stratified according to their mean disease activity during follow-up into being in low, moderate or high disease activity. Occurrences of strokes were analyzed within these strata with Kaplan-Meier-survival curves (Fig. 1).

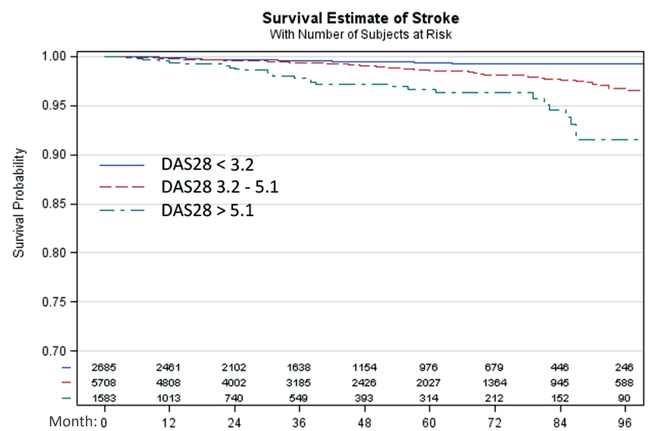
Conclusions

In addition to traditional risk factors for stroke such as age, male sex, smoking and hypertension, also atrial fibrillation increased the risk for stroke. This could have implications for the cardiovascular risk assessment in patients with RA.

A higher disease activity was significantly associated with the development of stroke. Patients with uncontrolled high disease activity over longer time periods are at increased risk for stroke.

In patients with equally controlled disease activity during follow-up the type of treatment has no impact on the risk of developing stroke.

Fig. 1: Development of stroke in patients stratified by their disease activity during follow-up.



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