CATEGORISING PATIENTS WITH RHEUMATOID ARTHRITIS USING TRAJECTORIES OF DISEASE ACTIVITY SCORE IN HUNGARY

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Introduction

Rheumatoid arthritis (RA) is a progressive, chronic, autoimmune disease, associated with polyarticular inflammation. Substantial proportion of patients with RA experience inflammatory pain which can entail joint swelling and also deformation of the inflamed area. A study of early RA patients identified using growth-based DAS28 trajectory modelling five mutually exclusive groups where these groups differed in the degree of radiographic progression, improvements of physical function and quality of life measures [1].

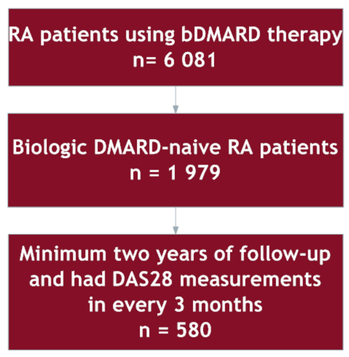
According to published data RA affects 0,5-1% of the adult population in industrialised countries. In Hungary approximately 50.000 people are involved in the disease [2].

The objective of the study was to categorise trajectories of disease activity in response to treatment to a new biologic DMARD measured by DAS28 score of bDMARD-naïve RA patients and to analyse whether these groups differ in demographic, disease-, treatment-related and cost variables.

Methods

Data source and study period: The retrospective analysis used patient-level healthcare utilization data from the National Health Insurance Fund of Hungary. The database contains all reimbursed health care services, demographic data on age, gender, date and location of birth/death and most importantly patient ID, type/date/place of service, International Classification of Diseases (ICD-10 codes) and International Classification of Health Interventions (ICHI) codes for in- and outpatient care or imaging technics. The actual results of laboratory tests, examinations or operations are not directly available. The study period spawned five years from 09.01.2012 to 12.31.2016.

Study population: The study population included those RA patients, who started their first bDMARD treatment during the study period, had at least two years of follow-up and had DAS28 measurements in every three month (Figure 1).



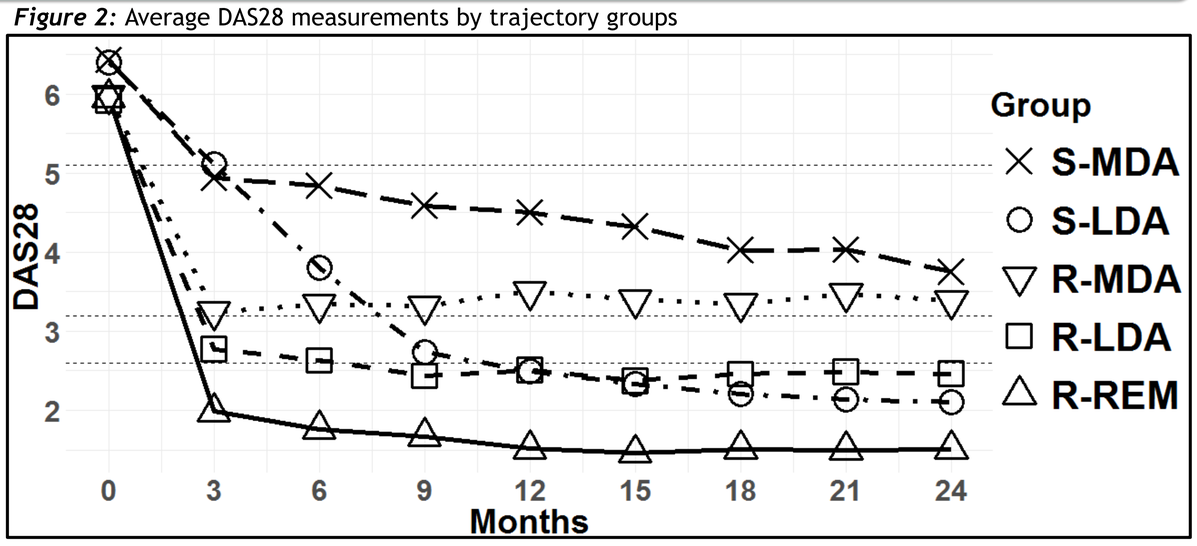
Statistical methods: Group-based trajectory modelling was applied to test for the existence of homogenous groups in the analysis. The distinct groups were determined by k-means clustering method for DAS28 trajectories using the kml package in R. The analysis was carried out in R (version 3.4.1), using kml package [3], which uses k-means clustering method for longitudinal data. After the classification the following characteristics were compared between the groups: gender, age, years elapsed between RA diagnosis and the start of the first bDMARD therapy, proportion of methotrexate therapy in combination with bDMARD therapy, proportion of patients achieving remission (DAS28 ≤ 2.6), total healthcare costs (in-,and outpatient costs, medical costs) and proportion of patients having knee or hip surgery during the two-year follow-up. The length of the first bDMARD therapy was analysed using Kaplan-Meier survival method, and the survival curves were compared by log rank test.

Results

By using trajectories clustering method the following 5 unique groups were detected (Figure 2):

- ***S-MDA:*** Slow improvement to moderate disease activity
- ***S-LDA:*** Slow improvement to low disease activity
- ***R-MDA:*** Rapid improvement to moderate disease activity
- ***R-LDA:*** Rapid improvement to low disease activity
- ***R-REM:*** Rapid improvement to remission

Figure 2: Average DAS28 measurements by trajectory groups



Comparing baseline characteristics:

- The proportion of female patients was highest (91.0%) in the S-LDA group and lowest (77.2%) in the R-REM group, but there was no significant difference between the proportions.
- There was no difference between the groups in the average age, and the median time elapsed between the RA diagnosis and start of the first bDMARD therapy.

Comparing treatment effectiveness and costs:

- Patients in the R-REM group achieved the highest remission rate (92.7%), while patients in the S-MDA group achieved the lowest remission rate (6.4%) within six months from the start of the first bDMARD therapy.
- Patients with slow disease activity score improvement had more knee and hip surgery in the first two years.
- The average healthcare cost was higher in every quarter year in the S-MDA and R-MDA groups relative to the S-LDA and R-LDA, R-REM groups (Table 1).

Figure 3: *Kaplan-Meier survival curves for persistence analysis*

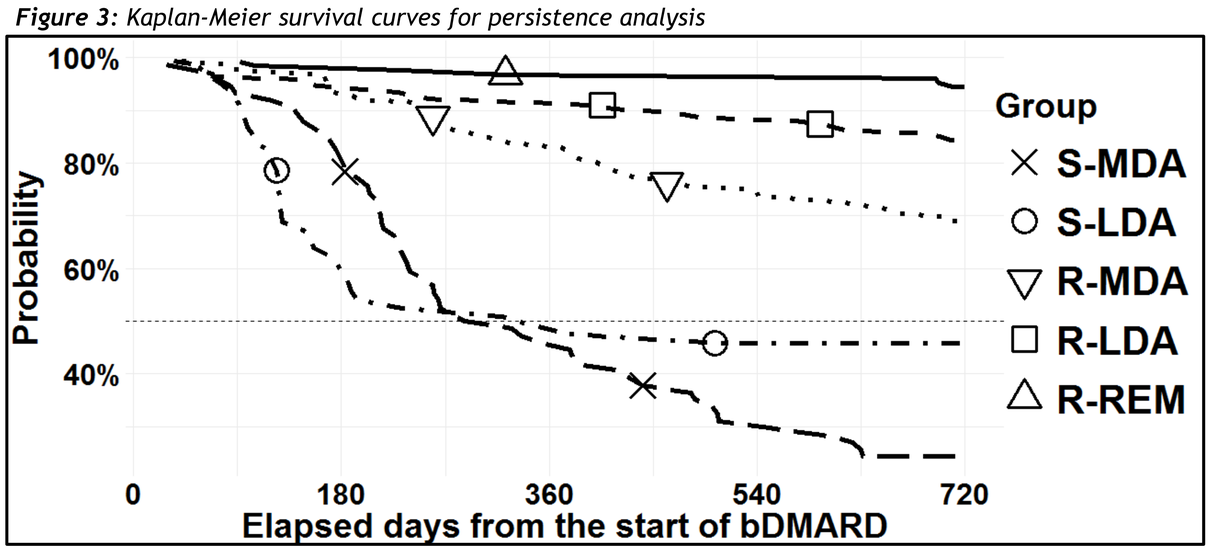


Table 1: Characteristics of the trajectory groups
(*Using Pearson's Chi-squared test, t-test and Mood's median test*)

	S-MDA n=78	S-LDA n=63	R-MDA n=152	R-LDA n=164	R-REM n=123	P-value
Female patients (%)						
	91.0%	84.1%	87.5%	86.0%	77.2%	0.063
Age, mean(sd)						
	52.46 (9.5)	49.95 (12.2)	52.28 (11.2)	51.96 (10.6)	50.84 (13.1)	0.555
Time between diagnosis and first bDMARD treatment, median (year)						
	3.36	3.82	4.76	4.55	5.26	0.35
Methotrexate combination therapy (%)						
	64.1%	39.7%	63.2%	60.4%	66.7%	0.006
Achieving remission (DAS28 ≤ 2.6) within 6 months (%)						
	6.4%	23.8%	32.2%	62.8%	92.7%	<0.001
Total healthcare costs in the first two years, median (€)						
	619 €	377 €	332 €	255 €	301 €	0.032
Knee and hip surgery within the two years (%)						
	9.0%	3.2%	1.3%	1.8%	0.8%	0.004

Comparing treatment related variables:

- The usage of methotrexate combination therapy was very similar across the cluster groups. In the cluster groups the proportion of methotrexate used in combinations with bDMARD therapy was around 60-66% except in the S-LDA group (39.7%).
- Patients with rapid improvement in the disease activity score stayed longer on the first biological treatment (Figure 3). Median therapy length was very similar in the S-MDA (at the 308th day) and S-LDA (at the 319th day) trajectory groups.

Conclusions

RA is a heterogeneous disease and DAS28 measurements in response to treatments can be used to determine distinct RA patient subgroups. These distinct disease trajectory groups are associated with various patient- and treatment-related variables, effectiveness and cost outcomes.

The significance of the measured differences between the groups are not clear yet. More extensive studies are needed to identify those factors at baseline that determine which trajectory the patient will follow during treatments.

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Poster code: PMS33