Early treatment response to csDMARD therapy in rheumatoid arthritis is a better predictor of low disease activity or treatment escalation at 12 and 24 months than autoantibodies or erosions

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EULAR 2017 SAT0674

Background & Objectives

The EULAR guidelines recommend using the presence of autoantibodies or erosions for treatment decisions[1]. The prognostic value of these factors regarding the primary treatment target in rheumatoid arthritis (RA), remission or low disease activity (LDA), is unclear.

The objective was to investigate biomarkers, csDMARD treatments and response to treatment regarding their usefulness to predict LDA or the need to escalate treatment within 24 months.

[1] Smolen et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2017

Patients & Methods

The control group of the prospectively followed German cohort RABBIT comprises patients who were enrolled at treatment start with csDMARDs after failure of at least one csDMARD therapy (N=2,983 after 2008). For this analysis, we excluded patients with less than 12 months observation time until data base closure at 31st October 2016, those with >2 csDMARD failures, and with a DAS28 <3.2 at enrolment. Those 180 patients, who were enrolled with less frequently used treatments (<4% of all) were additionally excluded.

We applied a multinomial generalized-estimating-equation (GEE) model to investigate:

(1) achievement of LDA at month 12/24 or

(2) treatment escalation to bDMARD in year one and two after enrolment.

Prognostic factors, treatment with csDMARDs and glucocorticoids as well as treatment response within 3-6 months were evaluated.

Results

In total, 1609 patients were included in the analysis. We found no major differences across treatment regimens except for patients treated with MTX + HCQ who had a lower DAS28, better physical function, a shorter disease duration and lower doses of glucocorticoids at treatment start.

Table 1: Baseline characteristics stratified by enrolment therapy.

	MTX mono	LEF mono	SSZ mono	MTX + LEF	MTX + SSZ	MTX + HCQ
N (%)	258 (16.0)	389 (24.2)	78 (4.9)	556 (34.6)	165 (10.2)	163 (10.1)
Female patients, n (%)	208 (80.6)	297 (76.3)	58 (74.4)	385 (69.2)	113 (68.5)	125 (76.7)
Age in years	59.0 (13.4)	60.1 (12.5)	62.0 (12.9)	58.0 (11.6)	58.1 (11.9)	60.0 (13.3)
Disease duration in years	6.2 (7.5)	5.8 (6.5)	5.9 (6.3)	5.6 (7.0)	5.1 (6.5)	4.7 (6.5)
DAS28	4.9 (1.0)	4.9 (1.0)	4.8 (1.0)	4.9 (1.0)	4.8 (1.0)	4.5 (0.8)
Erosions, n (%)	51 (19.8)	119 (30.6)	21 (26.9)	187 (33.6)	43 (26.1)	43 (26.4)
Seropositivity, n (%)	143 (55.4)	246 (63.2)	40 (51.3)	390 (70.1)	84 (50.9)	95 (58.3)
% of full physical function	69.8 (21.2)	67.4 (21.7)	68.8 (21.7)	70.0 (21.6)	69.8 (19.5)	76.2 (19.7)
≥3 comorbidities, n (%)	62 (24.0)	81 (20.8)	26 (33.3)	69 (12.4)	24 (14.5)	28 (17.2)
Glucocorticoids in mg/d	8.1 (10.2)	8.0 (9.6)	8.4 (10.9)	7.9 (9.3)	8.2 (12.9)	6.3 (10.2)
1 DMARD failure, n (%)	215 (83.3)	319 (82.0)	51 (65.4)	448 (80.6)	139 (84.2)	136 (83.4)
MTX failure, n (%)	33 (12.8)	380 (97.7)	69 (88.5)	529 (95.1)	104 (63.0)	135 (82.8)

Values are means (SD) unless otherwise specified.
Abbreviations: MTX – methotrexate; LEF – leflunomide; SSZ – sulfasalazine; HCQ – hydroxychloroquine; mono - monotherapy

Achievement of LDA or treatment escalation

Significant predictors for achieving LDA were low DAS28 at baseline, improvement in DAS28 within 3-6 months, better physical function and <3 comorbidities (Table 2). Compared to MTX mono, treatment with LEF mono decreased the chance for LDA achievement.

The probability for escalation to bDMARD therapy was significantly higher in younger patients, those with higher baseline DAS28 and with no improvement in DAS28 within 3-6 months. Concomitant glucocorticoid treatment in higher dosages and patients with <3 comorbidities further predicted treatment escalation. Switching to bDMARDs was most frequent in patients treated with MTX + LEF.

The presence of erosions or seropositivity was not associated with any of the outcomes.

Table 2: Results of the multinomial GEE-model at month 12 or 24.

	Achievement of LDA OR [95% CI]	Escalation of Therapy OR [95% CI]
Age (per 10 years)	0.98 [0.89; 1.07]	**0.74 [0.67; 0.81]**
Erosions (Yes vs. No)	1.03 [0.82; 1.30]	1.23 [0.93; 1.62]
Seropositivity (Yes vs. No)	0.84 [0.67; 1.06]	0.86 [0.66; 1.12]
DAS28 at Baseline (per unit)	**0.65 [0.58; 0.74]**	**1.18 [1.04; 1.35]**
DAS28 improvement (3-6 months, per unit)	**1.70 [1.54; 1.88]**	**0.83 [0.73; 0.94]**
Physical function (per 10 units)	**1.14 [1.08; 1.21]**	1.04 [0.98; 1.10]
≥ 3 comorbidities (vs. < 3)	**0.71 [0.53; 0.95]**	**0.67 [0.48; 0.94]**
Glucocorticoids (per 5 mg/d)	0.98 [0.82; 1.18]	**1.39 [1.19; 1.63]**
MTX mono (Reference)		
LEF mono	**0.71 [0.51; 0.99]**	1.39 [0.92; 2.10]
SSZ mono	0.88 [0.54; 1.45]	1.18 [0.61; 2.31]
MTX + LEF	0.73 [0.54; 1.00]	**1.80 [1.22; 2.65]**
MTX + SSZ	0.99 [0.67; 1.46]	1.13 [0.67; 1.91]
MTX + HCQ	1.08 [0.74; 1.59]	0.94 [0.54; 1.63]
Year 2 vs. Year 1	1.11 [0.85; 1.47]	1.17 [0.88; 1.55]

Conclusions

In patients with established RA, the highest impact on achieving LDA was found for disease activity (DAS28) at baseline and response to treatment within 3-6 months. Erosions and/or seropositivity were not associated with a poorer clinical outcome.

We thank all participating rheumatologists, especially those who enrolled the highest numbers of patients: Kaufmann J, Klopsch T, Eisterhues C, Braun J, Liebhaber A, Rockwitz K, Tony H, Krause A, Schwarze I, Gräßler A, Remstedt S, Berger S, Zinke S, Wilden E, Bussmann A, Ochs W, Burmester G, Bruckner A, Röser M, Richter C, Haas F, Bergerhausen H, Balzer S, Bohl-Bühler M, Wassenberg S, Kühne C, Fricke-Wagner H, Wiesmüller G, Harmuth W, Lebender S, Ständer E, Edelmann E, Tremel H, Stille C, Meier L, Müller L, Körber H, Kellner H, Krüger K, Thiele A, Krummel-Lorenz B, Kapelle A, Pick D, Kekow J, Hamann F, Möbius C, Manger K, Schmitt-Haendle M, Weiß K, Seifert A, Karberg K, Prothmann U, Feuchtenberger M, Aringer M, Krause D, Zänker M, Richter C, Reck A, Backhaus M, Burmester G, Schulze-Koops H, Grünke M, Eidner T, Zeh G, Dockhorn R, Herzberg C, Menne H, Dahmen G, von Hinüber U, Demary W, Heel N, Herzer P, Sörensen H, Roßbach A, Schneider M, Heel N, Wiesent F, Baumann C, Winkler K, Moosig F, Iking-Konert C, Euler H, Gause A, Max R, Blank N, Häntsch J, Alliger K, Gause A, Streibl H, Bielecke C, Bruns A, Hauser M, Schmidt R, Riechers E, Dexel T, Späthling-Mestekemper S, Höhle M, Möbius E, Schröder J

Funding: RABBIT is supported by a joint, unconditional grant from AbbVie, Bristol-Myers Squibb, Celltrion, Lilly, MSD Sharp & Dohme, Pfizer, Roche, Samsung Bioepis and UCB.

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