Patient journey analysis: A road to remission?

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SRQ

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Authors: Daniela Di Giuseppe (daniela.digiuseppe@ki.se)
Lotta Ljung (lotta.ljung@regionstockholm.se)

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1.0 Background and Rationale

1.1 Background

Rheumatoid arthritis (RA) is chronic polyarthritis, usually with symmetrical small joint involvement. Untreated joint inflammation in RA leads in many cases to destruction of bone and cartilage, pronounced functional impairments, pain, stiffness and chronic fatigue. In addition, patients with RA have an increased comorbidity, especially in the form of ischemic heart disease and an increased risk of premature death. The cause of RA is unknown. (1)

In Sweden, approximately 0.7% of the adult population is estimated to have RA, with approximately 40 new cases per 100,000 inhabitants per year. The disease can start at any age, but the majority of patients become affected between the ages of 50 and 70. It is 3 times more common among women than among men. (1)

Treatment aims to suppress RA disease activity – if possible, to clinical remission – to minimize the effects on the health in the short term as well as to prevent joint destruction and development of complications and comorbidity in the longer term. It is important to identify patients at high risk for persistent, serious disease early. Important principles in treatment strategies for early RA are early initiation of disease-modifying anti-rheumatic drugs (DMARDs), such as treatment with methotrexate in adequate doses, frequent check-ups and rapid changes in dose and medication in case of unsatisfactory effect. Remission as treatment target in RA is important for several aspects. (2)

Swedish national guidelines (SRF) and the standardized care flow for RA (Kunskapstyrningens vårdförlopp) targets DAS28 remission (DAS28<2.6) as a treatment goal. The standardized care flow in Sweden for RA was implemented in 2020 with the aim to support equal care for RA patients and with the objective of increasing the proportion of patients who are either in remission or low disease activity. (2,3)

Despite advanced systemic treatments, about a third of RA patients in Sweden do not achieve remission or low disease activity (DAS28<3.2), contrary to the national guideline which targets DAS28 remission (DAS28<2.6).

There is evidence suggesting that a more targeted treatment approach and switching to another mode of action could improve patient outcomes. (4) This analysis aims to clarify these aspects by answering specific questions such as the proportion of patients who do not reach DAS28 remission, the time it takes for patients to reach this state, the duration before patients who don't achieve remission receive the next line of treatment, and the proportion of patients who switch to a different treatment mode.

DAS28 – Disease Activity Score (DAS) is an activity index in which the number of swollen and tender joints, SR or CRP and the patient's global evaluation of the state of health (VAS scale) are included. The most used variant is based on assessment of 28 joints. (2)

The Swedish Rheumatology Quality Register (SRQ) is a national register with the aim of improving treatment and follow-up of patients with rheumatic disease. The registry was initiated in 1995 and currently covers over 100 rheumatic diagnoses and 89 000 active patients. Data in the register is inserted by health care professionals, and by patients through PER – The Patient's Self Registration (prior to every visit).

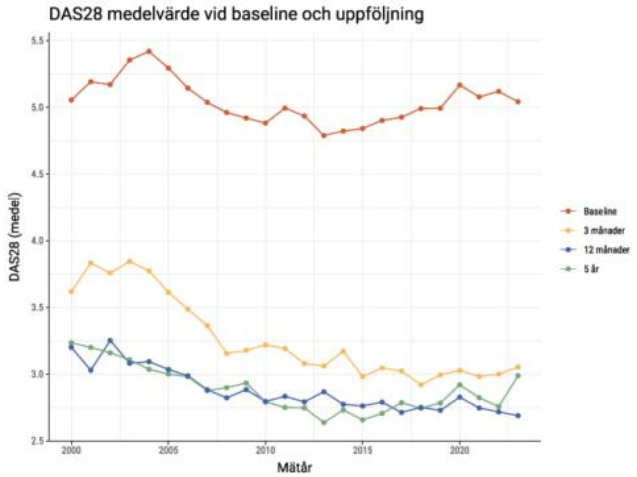
Recently, data has been published by SRQ of the mean outcome of DAS 28 in newly debuted RA at baseline and at 3 months, 12 months and 5 years follow-up, between years 2000 and 2023. (5)

Disease activity is lower at follow-up visits compared to the baseline visit, and there is a clear trend towards lower DAS28-values between 2000 and 2010. Between the years 2010 and 2023 the mean DAS28-values are stable with some fluctuation. The mean DAS 28 values are also higher at 3-month follow-up compared to 12 months and 5 years follow-up.

The mean DAS28 values at 12 months and 5 years follow-up fluctuates between 2,6 and 3,0 in between 2010 and 2023. This is in line with previously published outcomes on the level of DAS28-response from the registry. About a third of the of Swedish patients with RA treated with advanced systemic treatments do not reach remission or low disease activity (DAS28<3.2), despite the treatment goal according to national guidelines is DAS28 remission (DAS28<2.6). (5)

The improvement in DAS28 results between 2000 and 2010 seen in the graph below coincides with the introduction of TNF-inhibitors for treatment of RA. As pointed out in

the publication, no clear improvement after the latest improvement in available treatment options can be seen in the graph, and this is worth further analysis.(5)



Mean DAS28-values at baseline and follow-up.

1.2 Rationale

The proportion of patients with RA treated with advanced systemic or biological treatments that over time reach different levels of DAS28 response (remission (DAS28 <2.6), low disease activity (LDA, 2.6<=DAS28<=3.2) and high disease activity (HDA, DAS28 >3.2), in Swedish clinical practice is not fully understood. Currently available data describes the proportion of patients reaching LDA or remission, or the median DAS 28 values over time.

By further differentiating treatment outcomes, the proportion of patients that reach the treatment goal of remission have been described, which in turn can be used to evaluate the outcomes of the treatment of RA patients in Swedish clinical practice.

In addition, the treatment switching patterns have been investigated to better understand patients' treatment journeys. For a patient starting advanced systemic treatment, what is the overall response rate for DAS28 remission over the first three years of treatment? How many lines of treatment will they receive? How long will it take to reach remission? Which proportion of patients do not reach remission or LDA over the first three years of remission?

2.0 Research Questions

- Which is the proportion of patients that reach DAS28 remission, LDA and HDA overall and per treatment line at 6, 12, 18, 24, 30 and 36 months after initiation of the first b/tsDMARD.

- Which proportion of patients per disease activity level at each timepoint (6, 12, 18 24, 30 and 36 months) switch treatment, to the same (excluding non-medical switch) or to another mode of action?

- How many lines of treatment have the patients received per final disease activity level (DAS28 remission, LDA and HDA) at the end of the follow-up period?

- What is the time to DAS28 remission for the proportion of patients that reach DAS28 remission during the follow-up period?

- Among those not in remission at the 3 months and 6 months visit respectively, how many switched at 3, 6, 12, 18, 24, 30 and 36 months?

2.1 Study Endpoints

- The proportion of patients with DAS28 remission, LDA and HDA overall and per treatment line.
- The proportion of patients with DAS28 remission, LDA and HDA overall over time.
- The proportion of patients that switch treatment to another mode of action, overall and per treatment line.
- Time to DAS28 remission.
- The proportion of patients that switch treatment over time, of those patients that are not in remission after 3 and 6 months respectively.
- Description of clinical characteristics, per treatment line and outcome (DAS28 remission, LDA and HDA).

3.0 Methods

This is an analysis of observational data collected in the Swedish Rheumatology Quality registry (SRQ).

Adult patients with a diagnosis of RA initiating first line treatment with a b/tsDMARD between 2018 and 2021 have been included in the study and followed for 36 months. Data on treatment outcomes measured as DAS28, treatment switches and reason for discontinuation have been collected at 6, 12, 18, 24, 30 and 36 months after treatment initiation.

3.1 Population

This is an observational quality register analysis. The following inclusion and exclusion criteria have been used to define the patient population:

- ≥ 18 years of age with a diagnosis of RA (M05 and M06)
- initiated treatment with a first b/tsDMARD (as listed in 3.2.2) between 2018 and 2021.
- has a minimum follow-up time since the start of the first treatment of 36 months.

Exclusion criteria:

- None

3.2 Description of data collection

3.2.1 Data Source

Only data from the SRQ have been included in this report.

3.2.2 Variables included

The following data was analyzed at baseline (start of first b/tsDMARD):

1. Demographics:
- Age
- Sex

2. Clinical characteristics:
- Disease duration
- Rheumatoid factor

- Anticitrullinated protein antibodies [anti-CCP]
- b/tsDMARD treatment:
    - TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab)
    - JAKi (baricitinib, filgotinib, tofacitinib, upadacitinib)
    - Other:
        - IL-6i (sarilumab, tocilizumab)
        - CTLA4-Ig (abatacept)
        - CD20i (rituximab)
        - IL-1i (anakinra)

- Concomitant use of csDMARD:
    - Methotrexate
    - Other csDMARD (Sulfasalazine, hydroxychloroquine, cyclosporine A, leflunomide)
- Concomitant use of GCs (prednisolone)
- Disease Activity Score (DAS28) based on ESR.
- Clinical Disease Activity Index (CDAI)
- HAQ score
- Pain (VAS)
- Reason for stopping/switching treatment

The following data was analyzed at 6, 12, 18, 24, 30 and 36 months:

- b/tsDMARD treatment:
    - TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab)
    - JAKi (baricitinib, filgotinib, tofacitinib, upadacitinib)
    - Other:
        - IL-6i (sarilumab, tocilizumab)
        - CTLA4-Ig (abatacept)
        - CD20i (rituximab)
        - IL-1i (anakinra)
- Disease Activity Score (DAS) based on SR or CRP
- Pain (VAS)
- HAQ-score
- CDAI
- Reason for stopping/switching treatment

3.2.3 Data Collection Methods

Time-points

The baseline date was defined as the date for first prescription ("ordination") of a b/tsDMARD registered. Data for the baseline characteristics have been collected among the visits within -30; +30 days from the baseline date. Data for follow-up timepoints have been collected at 6, 12, 18, 24, 30 and 36 months after the baseline date.

For the follow-up timepoints data availability depends on clinical practice visit patterns and therefore the following time windows for the evaluation timepoints have been used in the data collection:

Follow-up time (months* after baseline)	Time window (number of days after baseline)
6	180 ± 90 days
12	360 ± 90 days
18	540 ± 90 days
24	720 ± 90 days
30	900 ± 90 days
36	1080 ± 90 days

*1 month is equal to 30 days.

Only visits with non-missing DAS28 have been included. If multiple follow-up visits are available within the same time- window, the visit with non-missing DAS28 closest to the follow-up time will be collected.

For the analysis presented in table 7, the windows were slightly different, with 3 months defined as visits between 30 and 120 days and 6 months as 120 to 270 days.

Definition of treatment discontinuation

Patients are assumed to be on prescribed treatment until start of another b/tsDMARD treatment is prescribed or until treatment discontinuation is registered in the registry.

Definition of treatment switch

Patients are assumed to have switched treatment if another b/tsDMARD is prescribed. Non-medical switches between treatments with the same substance or a biosimilar are not considered switches in this analysis.

3.3 Statistical Analysis

Descriptive statistics for continuous variables will be presented as medians (IQR and min, max). Categorical variables will be presented as frequencies and percentages.

In addition, 95% confidence intervals for proportions and means will be calculated.

Time-to-event data will also be analyzed using the method of Kaplan and Meier.

All analyses have been performed using SAS 9.4.

4.0 Results

Descriptive characteristics of the included patients are presented in table 1.

A total of 5914 patients were included in this report, of which the majority were treated with a TNFi as first b/tsDMARD (83.0%). Another 6.2% started a JAKi and 10.8% a non-TNFi bDMARD as their first ever b/tsDMARD. Patients who started a TNFi as first treatment were younger (57 years old) than those starting a JAKi (64 years) or non-TNFi bDMARD (66 years). Patients starting a JAKi were more likely to be women (78.6% vs. TNFi 75.1% and non-TNFi bDMARD 71.6%).

TNFi starters had a shorter disease duration compared to the other 2 groups, and higher previous use of methotrexate.

Table 1. Baseline patient characteristics at start of first b/tsDMARD

	All	TNFi	JAKi	Other
N	5915	4909	364	642
Age	58.0 (47.0-69.0)	57.0 (46.0-68.0)	64.0 (52.5-73.0)	66.0 (54.0-74.0)
Female sex n (%)	4431 (74.9)	3686 (75.1)	286 (78.6)	459 (71.5)
Disease duration, median, years (IQR)	2.4 (0.6-7.7)	2.3 (0.6-7.4)	3.8 (0.9-9.4)	2.7 (0.7-8.7)
Rheumatoid factor positivity, n (%)	1954 (69.4)	1643 (69.3)	103 (66.5)	209 (72.3)
Anticitrullinated protein antibodies positivity, n (%)	2240 (81.2)	1903 (81.5)	117 (79.1)	220 (79.1)
Disease activity scores (DAS28), median (IQR)	4.5 (3.6-5.3)	4.4 (3.6-5.3)	4.5 (3.4-5.4)	4.6 (3.7-5.7)
Clinical Disease Activity Index (CDAI) , median (IQR)	19.0 (13.0-26.5)	19.0 (13.0-26.0)	18.0 (12.5-27.0)	21.0 (14.0-28.0)
Pain (VAS), mm, median (IQR)	55.0 (33.0-73.0)	55.0 (33.0-72.0)	52.5 (27.5-71.5)	53.0 (34.0-77.0)
ESR, mm/h, median (IQR)	18.0 (9.0-33.0)	18.0 (9.0-32.0)	18.0 (10.0-38.0)	26.0 (12.0-44.0)
CRP, g/L, median (IQR)	5.0 (2.4-15.0)	5.0 (2.3-14.0)	6.0 (3.0-20.0)	7.0 (3.0-24.0)
Swollen joints, 28-joint count, median (IQR)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	3.0 (1.0-6.0)	4.0 (2.0-7.0)
Tender joints, 28-joint count, median (IQR)	5.0 (2.0-8.0)	5.0 (2.0-8.0)	4.0 (2.0-8.0)	5.0 (2.0-8.5)
HAQ score, median (IQR)	0.9 (0.4-1.3)	0.8 (0.4-1.3)	0.9 (0.4-1.5)	0.9 (0.5-1.4)
Previous MTX, n (%)	4621 (78.1)	3933 (80.1)	268 (73.6)	421 (65.6)
Previous non-MTX csDMARD, n (%)	1883 (31.8)	1551 (31.6)	110 (30.2)	222 (34.6)
Previous use of GC, n (%)	2879 (48.7)	2379 (48.5)	165 (45.3)	335 (52.3)
Smoker, n (%)	283 (12.5)	248 (12.7)	15 (12.3)	20 (11.0)

Results on the first research questions (proportion of patients that reach DAS28 remission, LDA and HDA overall and per treatment line at 6, 12, 18, 24, 30 and 36 months after initiation of the first b/tsDMARD.) are presented in table 2.

Among the patients with a 6 months visit (n=2884), close to half of the patients were in remission at 6 months (46.0%), but a high percentage were still in a state with HDA (37.1%). Only a small minority of the patients did a treatment switch at 6 months, ranging from 4% for those in remission to 9% for those with HDA. Those who switched, mainly switched from a TNFi to a second TNFi. Looking only to those who have switched, i.e. have started a second or third treatment before the 6 months visit (n=176), 31.8% were in remission, while 52.3% were in HDA.

Only 1760 patients had a visit at 12 months. Similar percentages at 6 months of disease activity were also observed at 12 months, but the proportion of patients changing treatment was now higher, from 18.6% among patients in remission to 24.7% for patients in HDA. Patients who were on second treatment most often had a second TNFi following a first ever TNFi (10% of LDA and HDA patients). A higher percentage of patients reached remission at 12 months after switch (39.2%), and less were in HDA (43.5%) compared with 6 months. Change of mode-of-action were more frequent among patients in HDA.

The number of patients with available information on DAS28 was decreasing with time (n=1514 at 18 months, n=1310 at 24 months, n=1286 at 30 months, and n=1229 at 36 months). However, the distribution of DAS28 remained very similar across time. The proportion of patients switching increased with time, with TNFi as second choice after a TNFi remaining as the most used option. However, as third line choice, non-TNFi bDMARD was preferred to TNFi and JAKi, after failure of 2 other TNFi treatments.

Table 2. Treatment switches

		6 months			12 months			18 months			24 months			30 months			36 months		
		Remis-sion	LDA	HDA	Remis-sion	LDA	HDA	Remis-sion	LDA	HDA	Remis-sion	LDA	HDA	Remis-sion	LDA	HDA	Remis-sion	LDA	HDA
	All patients, n (%)	1328 (46.0)	485 (16.8)	1071 (37.1)	773 (43.9)	292 (16.6)	695 (39.5)	686 (45.3)	248 (16.4)	580 (38.3)	609 (46.5)	225 (17.2)	476 (36.3)	616 (47.9)	224 (17.4)	446 (34.7)	556 (45.2)	221 (18.0)	452 (36.8)
Treatment switches	Proportion of patients with treatment switch, n (%)	56 (4.2)	30 (6.2)	92 (8.6)	144 (18.6)	62 (21.2)	172 (24.7)	137 (20.0)	73 (29.4)	216 (37.2)	164 (26.9)	65 (28.9)	209 (43.9)	172 (27.9)	80 (35.7)	213 (47.8)	183 (32.9)	76 (34.4)	213 (47.1)
	Number of switches per patient (median, IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
1L treatment	**TNFi, n (%)**	1095 (82.5%)	383 (79.0%)	799 (74.6%)	512 (66.2%)	201 (68.8%)	414 (59.6%)	454 (66.2%)	148 (59.7%)	299 (51.6%)	373 (61.3%)	127 (56.4%)	200 (42.0%)	365 (59.3%)	108 (48.2%)	186 (41.7%)	315 (56.6%)	112 (50.7%)	190 (42.0%)
	JAKi, n (%)	63 (4.7%)	25 (5.2%)	59 (5.5%)	35 (4.5%)	8 (2.7%)	35 (5.0%)	26 (3.8%)	10 (4.0%)	18 (3.1%)	19 (3.1%)	11 (4.9%)	21 (4.4%)	28 (4.6%)	11 (4.9%)	15 (3.4%)	19 (3.4%)	17 (7.7%)	22 (4.9%)
	Other n (%)	114 (8.6%)	48 (9.9%)	121 (11.3%)	83 (10.7%)	21 (7.2%)	75 (10.8%)	70 (10.2%)	17 (6.9%)	49 (8.4%)	55 (9.0%)	22 (9.8%)	46 (9.7%)	56 (9.1%)	25 (11.2%)	34 (7.6%)	40 (7.2%)	16 (7.2%)	32 (7.1%)
2L	**TNFi => TNFi, n (%)**	29 (2.2%)	11 (2.3%)	56 (5.2%)	56 (7.2%)	29 (9.9%)	73 (10.5%)	50 (7.3%)	28 (11.3%)	92 (15.9%)	48 (7.9%)	27 (12.0%)	74 (15.6%)	53 (8.6%)	30 (13.4%)	67 (15.0%)	53 (9.5%)	19 (8.6%)	74 (16.4%)
	TNFi => JAKi, n (%)	12 (0.9%)	8 (1.7%)	14 (1.3%)	20 (2.6%)	8 (2.7%)	20 (2.9%)	20 (2.9%)	13 (5.2%)	21 (3.6%)	19 (3.1%)	3 (1.3%)	17 (3.6%)	20 (3.3%)	6 (2.7%)	14 (3.1%)	24 (4.3%)	9 (4.1%)	13 (2.9%)
	TNFi => Other, n (%)	11 (0.8%)	4 (0.8%)	16 (1.5%)	31 (4.0%)	9 (3.1%)	21 (3.0%)	21 (3.1%)	14 (5.6%)	29 (5.0%)	34 (5.6%)	10 (4.4%)	35 (7.4%)	32 (5.2%)	5 (2.2%)	30 (6.7%)	28 (5.0%)	12 (5.4%)	17 (3.8%)
	JAKi=>TNFi, n (%)	1 (0.1%)	0	2 (0.2%)	3 (0.4%)	0	4 (0.6%)	3 (0.4%)	1 (0.4%)	4 (0.7%)	3 (0.5%)	2 (0.9%)	1 (0.2%)	1 (0.2%)	1 (0.4%)	5 (1.1%)	2 (0.4%)	1 (0.5%)	1 (0.2%)
	JAKi=>JAKi, n (%)	0	0	0	0	1 (0.3%)	0	1 (0.2%)	0	2 (0.3%)	0	0	1 (0.2%)	0	1 (0.4%)	2 (0.4%)	2 (0.4%)	1 (0.5%)	2 (0.4%)
	JAKi=>Other, n (%)	0	1 (0.2%)	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.3%)	0	1 (0.2%)	0	0	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (0.2%)	1 (0.5%)	0
	Other => TNFi, n (%)	1 (0.1%)	0	1 (0.1%)	2 (0.3%)	1 (0.3%)	5 (0.7%)	3 (0.4%)	1 (0.4%)	3 (0.5%)	3 (0.5%)	1 (0.4%)	6 (1.3%)	1 (0.2%)	1 (0.4%)	4 (0.9%)	3 (0.5%)	3 (1.4%)	2 (0.4%)
	Other=> JAKi, n (%)	1 (0.1%)	0	0	1 (0.1%)	0	2 (0.3%)	3 (0.4%)	2 (0.8%)	0	1 (0.2%)	1 (0.4%)	3 (0.6%)	1 (0.2%)	1 (0.4%)	0	1 (0.2%)	0	4 (0.9%)
	Other=> Other, n (%)	0	2 (0.4%)	0	3 (0.4%)	1 (0.3%)	2 (0.3%)	4 (0.6%)	1 (0.4%)	6 (1.0%)	7 (1.2%)	0	5 (1.1%)	4 (0.7%)	2 (0.9%)	4 (0.9%)	6 (1.1%)	4 (1.8%)	4 (0.9%)

3L	**TNFi => TNFi => TNFi, n (%)**	1 (0.1%)	0	1 (0.1%)	4 (0.5%)	4 (1.4%)	7 (1.0%)	2 (0.3%)	1 (0.4%)	11 (1.9%)	4 (0.7%)	5 (2.2%)	11 (2.3%)	7 (1.1%)	6 (2.7%)	19 (4.3%)	13 (2.3%)	5 (2.3%)	24 (5.3%)
	TNFi => TNFi => JAKi, n (%)	0	0	1 (0.1%)	7 (0.9%)	4 (1.4%)	6 (0.9%)	7 (1.0%)	5 (2.0%)	10 (1.7%)	13 (2.1%)	3 (1.3%)	10 (2.1%)	9 (1.5%)	4 (1.8%)	12 (2.7%)	15 (2.7%)	6 (2.7%)	17 (3.8%)
	TNFi => TNFi => Other, n (%)	0	2 (0.4%)	0	8 (1.0%)	3 (1.0%)	10 (1.4%)	8 (1.2%)	4 (1.6%)	15 (2.6%)	12 (2.0%)	8 (3.6%)	17 (3.6%)	16 (2.6%)	12 (5.4%)	23 (5.2%)	17 (3.1%)	7 (3.2%)	16 (3.5%)

Reason of discontinuations by line of treatment and treatment group are presented in Table 3. The most common reason for discontinuation overall was lack of efficacy. For 1st line of therapy, other reasons were the most frequent reason for discontinuation of JAKi or other bDMARDs. There was a tendency of an increasing proportion of patients stopping a 2nd or 3rd line of treatment due to lack of efficacy.

Table 3. Treatment discontinuation

		6 months			12 months			18 months			24 months			30 months			36 months		
		Lack/ loss of efficacy, n/N (%)	AE, n/N (%)	Other, n/N (%)	Lack/ loss of efficacy, n/N (%)	AE, n/N (%)	Other, n/N (%)	Lack/ loss of efficacy, n/N (%)	AE, n/N (%)	Other, n/N (%)	Lack/ loss of efficacy, n/N (%)	AE, n/N (%)	Other, n/N (%)	Lack/ loss of efficacy, n/N (%)	AE n/N (%)	Other, n/N (%)	Lack/ loss of efficacy , n (%)	AE, n (%)	Other, n (%)
1L treatment	TNFi, n (%)	592 (49.5%)	202 (16.9%)	402 (33.6%)	260 (44.7%)	109 (18.7%)	213 (36.6%)	165 (39.6%)	69 (16.6%)	183 (43.9%)	111 (40.7%)	48 (17.6%)	114 (41.8%)	79 (30.4%)	42 (16.2%)	139 (53.5%)	90 (38.6%)	40 (17.2%)	103 (44.2%)
	JAKi n (%)	25 (29.8%)	24 (28.6%)	35 (41.7%)	18 (42.9%)	11 (26.2%)	13 (31.0%)	7 (26.9%)	7 (26.9%)	12 (46.2%)	6 (24.0%)	6 (24.0%)	13 (52.0%)	7 (33.3%)	5 (23.8%)	9 (42.9%)	5 (20.0%)	7 (28.0%)	13 (52.0%)
	Other n (%)	49 (34.0%)	24 (16.7%)	71 (49.3%)	19 (21.1%)	14 (15.6%)	57 (63.3%)	14 (23.3%)	10 (16.7%)	36 (60.0%)	11 (23.4%)	4 (8.5%)	32 (68.1%)	11 (24.4%)	9 (20.0%)	25 (55.6%)	7 (24.1%)	4 (13.8%)	18 (62.1%)
2L	TNFi, n (%)	50 (65.8%)	10 (13.2%)	16 (21.1%)	72 (61.0%)	20 (16.9%)	26 (22.0%)	63 (52.9%)	24 (20.2%)	32 (26.9%)	46 (52.9%)	14 (16.1%)	27 (31.0%)	37 (44.6%)	13 (15.7%)	33 (39.8%)	28 (41.8%)	14 (20.9%)	25 (37.3%)
	JAKi n (%)	9 (50.0%)	2 (11.1%)	7 (38.9%)	10 (41.7%)	5 (20.8%)	9 (37.5%)	11 (40.7%)	8 (29.6%)	8 (29.6%)	7 (58.3%)	3 (25.0%)	2 (16.7%)	6 (42.9%)	1 (7.1%)	7 (50.0%)	8 (47.1%)	1 (5.9%)	8 (47.01%)
	Other n (%)	12 (57.1%)	3 (14.3%)	6 (28.6%)	20 (54.1%)	5 (13.5%)	12 (32.4%)	21 (61.8%)	4 (11.8%)	9 (26.5%)	13 (41.9%)	6 (19.4%)	12 (38.7%)	12 (48.0%)	5 (20.0%)	8 (32.0%)	10 (38.5%)	5 (19.2%)	11 (42.3%)
3L	TNFi, n (%)	1 (33.3%)	2 (66.7%)	0 (0.0%)	9 (60.0%)	4 (26.7%)	2 (13.3%)	6 (85.7%)	1 (14.3%)	0 (0.0%)	10 (58.8%)	5 (29.4%)	2 (11.8%)	10 (43.5%)	6 (26.1%)	7 (30.4%)	9 (60.0%)	5 (33.3%)	1 (6.7%)
	JAKi n (%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	12 (75.0%)	3 (18.7%)	1 (6.3%)	8 (61.5%)	0 (0.0%)	5 (38.5%)	7 (50.0%))	2 (14.3%)	5 (35.7%)	11 (57.9%)	2 (10.5%)	6 (31.6%)	8 (50.0%)	2 (12.5%)	6 (37.5%)
	Other n (%)	1 (50.0%)	0 (0.0%)	1 (50.0%)	3 (21.4%)	4 (28.6%)	7 (50.0%)	7 (46.7%)	3 (20.0%)	5 (33.3%)	8 (53.3%)	2 (13.3%)	5 (33.3%)	14 (58.3%)	5 (20.8%)	5 (20.8%)	9 (50.0%)	4 (22.2%)	5 (27.8%)

Clinical characteristics of the patients in table 2 at each time point are presented in table 4. Patients with a recorded DAS28 at 12 months had a slightly shorter disease duration compared to the other time points. Disease duration was not clearly shorter for patients in remission, even if that pattern was observed at 18, 24 and 30 months.

Patients with LDA were more likely to have RF, and patients in remission or LDA were more likely to have positive ACPA. Patients with HDA had higher median VAS for pain than patients with LDA or remission, but the difference in VAS pain scores between patients with LDA and remission were also marked. A similar pattern was observed for HAQ.

Regarding the use of concomitant treatments, patients in remission were more likely to have a concomitant use of methotrexate, while patients with HDA had a lower use of methotrexate, but higher use of other csDMARDs and corticosteroids.

Table 4. Clinical outcomes and concomitant drug use

		6 months			12 months			18 months			24 months			30 months			36 months		
		Remission	LDA	HDA	Remission	LDA	HDA	Remission	LDA	HDA	Remission	LDA	HDA	Remission	LDA	HDA	Remission	LDA	HDA
	All patients, n/N (%)	1328 (46.0)	485 (16.8)	1071 (37.1)	773 (43.9)	292 (16.6)	695 (39.5)	686 (45.3)	248 (16.4)	580 (38.3)	609 (46.5)	225 (17.2)	476 (36.3)	616 (47.9)	224 (17.4)	446 (34.7)	556 (45.2)	221 (18.0)	452 (36.8)
Clinical outcomes	**Disease duration, years**	2.0 (0.5-6.9)	2.5 (0.5-7.7)	1.9 (0.5-7.6)	1.6 (0.4-6.4)	1.6 (0.4-5.5)	1.5 (0.4-6.5)	1.5 (0.4-7.4)	2.0 (0.5-5.9)	1.9 (0.5-7.4)	1.7 (0.5-6.2)	2.2 (0.5-6.9)	2.3 (0.6-7.9)	1.9 (0.6-7.0)	2.4 (0.6-7.9)	2.3 (0.6-8.1)	2.3 (0.6-7.6)	2.3 (0.6-7.8)	2.1 (0.6-7.3)
	Rheumatoid factor	491 (66.7)	189 (72.7)	361 (67.6)	296 (70.3)	124 (74.7)	252 (67.7)	250 (64.9)	100 (79.4)	206 (67.3)	237 (67.9)	85 (77.3)	172 (66.4)	220 (64.7)	79 (71.8)	155 (70.5)	201 (67.0)	82 (68.3)	176 (71.8)
	Anticitrullinated protein antibodies	575 (79.6)	212 (83.5)	411 (78.9)	334 (81.3)	137 (84.6)	286 (78.4)	313 (83.0)	102 (82.3)	215 (71.4)	283 (82.5)	85 (79.4)	202 (79.2)	271 (80.7)	88 (82.2)	163 (75.5)	241 (81.1)	96 (80.7)	189 (78.8)
	Disease activity scores (DAS28)	1.9 (1.4-2.2)	2.9 (2.7-3.0)	4.1 (3.6-4.8)	1.8 (1.4-2.2)	2.9 (2.8-3.1)	4.3 (3.7-5.1)	1.8 (1.3-2.2)	2.9 (2.7-3.0)	4.1 (3.7-4.8)	1.9 (1.4-2.2)	2.9 (2.7-3.0)	4.1 (3.7-4.9)	1.9 (1.4-2.2)	2.9 (2.7-3.0)	4.1 (3.6-4.8)	1.9 (1.4-2.2)	2.9 (2.7-3.0)	4.1 (3.6-4.9)
	Clinical Disease Activity Index (CDAI)	3.0 (1.0-5.5)	6.5 (4.5-9.0)	14.3 (10.5-21.0)	2.5 (0.0-5.0)	7.5 (5.0-9.5)	16.0 (10.5-23.0)	2.5 (0.0-4.5)	6.5 (4.5-8.5)	14.5 (10.5-20.5)	2.5 (0.0-4.5)	6.5 (4.5-9.5)	14.5 (9.5-21.5)	2.5 (0.0-5.0)	6.5 (4.5-9.5)	14.5 (10.0-21.0)	2.5 (0.0-4.5)	6.0 (4.0-9.5)	14.5 (9.5-21.0)
	Pain (VAS)	10.0 (3.0-25.0)	28.0 (11.0-49.0)	49.0 (29.0-69.0)	11.0 (3.0-25.5)	31.0 (18.0-52.0)	55.0 (33.0-72.0)	13.0 (3.0-30.0)	28.0 (10.0-50.0)	52.0 (31.0-71.0)	13.0 (4.0-30.0)	31.0 (14.0-49.0)	55.0 (34.5-73.0)	14.0 (5.0-31.0)	30.0 (18.0-52.0)	55.0 (35.0-71.0)	13.0 (4.0-26.0)	30.0 (14.0-50.0)	54.0 (37.0-70.0)
	ESR	7.0 (3.0-12.0)	14.0 (8.0-24.0)	20.0 (12.0-32.0)	7.0 (3.0-12.0)	13.0 (7.0-21.0)	21.0 (12.0-36.0)	7.0 (4.0-12.0)	14.5 (8.0-27.0)	20.0 (11.0-32.0)	7.0 (4.0-12.0)	15.0 (9.0-25.0)	22.0 (12.0-38.0)	7.0 (4.0-12.0)	15.0 (8.0-25.0)	21.0 (11.0-35.0)	7.0 (4.0-12.0)	17.0 (10.0-27.0)	21.0 (12.0-34.0)
	CRP	2.0 (1.0-4.0)	4.0 (1.2-5.0)	5.0 (2.0-10.0)	2.0 (1.0-4.0)	3.0 (1.0-5.0)	5.0 (2.2-11.0)	2.0 (1.0-4.0)	3.1 (1.0-5.0)	4.1 (2.0-9.0)	2.4 (1.0-4.0)	3.7 (1.0-5.9)	5.0 (2.0-11.0)	2.1 (1.0-4.0)	3.9 (1.7-5.0)	4.0 (2.0-10.0)	2.0 (1.0-4.0)	4.0 (2.0-5.5)	4.0 (2.0-7.4)
	Swollen joints	0.0 (0.0-0.0)	0.0 (0.0-1.0)	2.0 (1.0-4.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	2.0 (1.0-5.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	2.0 (0.0-4.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	2.0 (0.0-4.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	2.0 (0.0-4.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	2.0 (0.0-4.0)
	Tender joints	0.0 (0.0-0.0)	1.0 (0.0-2.0)	4.0 (2.0-7.0)	0.0 (0.0-0.0)	1.0 (0.0-2.0)	4.0 (2.0-8.0)	0.0 (0.0-0.0)	1.0 (0.0-2.0)	4.0 (2.0-7.0)	0.0 (0.0-0.0)	1.0 (0.0-2.0)	4.0 (2.0-7.0)	0.0 (0.0-0.0)	0.0 (0.0-2.0)	3.0 (2.0-6.0)	0.0 (0.0-0.0)	0.0 (0.0-2.0)	4.0 (2.0-7.0)
	HAQ score	0.3 (0.0-0.5)	0.5 (0.3-1.0)	0.9 (0.5-1.3)	0.1 (0.0-0.5)	0.6 (0.3-0.9)	1.0 (0.6-1.3)	0.1 (0.0-0.6)	0.5 (0.1-0.9)	0.9 (0.5-1.4)	0.1 (0.0-0.5)	0.5 (0.1-0.9)	1.0 (0.5-1.4)	0.3 (0.0-0.6)	0.6 (0.1-1.0)	1.0 (0.5-1.4)	0.1 (0.0-0.6)	0.6 (0.1-0.9)	1.0 (0.5-1.4)

Concomitant drug use	**Concomitant use of MTX, n (%)**	835 (62.9)	273 (56.3)	618 (57.7)	440 (56.9)	173 (59.2)	367 (52.8)	385 (56.1)	133 (53.6)	305 (52.6)	322 (52.9)	126 (56.0)	221 (46.4)	347 (56.3)	115 (51.3)	209 (46.9)	309 (55.6)	102 (46.2)	199 (44.0)
	Concomitant use of csDMARD, n (%)	111 (8.4)	54 (11.1)	110 (10.3)	74 (9.6)	31 (10.6)	76 (10.9)	70 (10.2)	28 (11.3)	74 (12.8)	57 (9.4)	27 (12.0)	69 (14.5)	51 (8.3)	34 (15.2)	54 (12.1)	44 (7.9)	20 (9.0)	76 (16.8)
	Concomitant use of GC, n (%)	316 (23.8)	152 (31.3)	411 (38.4)	154 (19.9)	86 (29.5)	257 (37.0)	112 (16.3)	63 (25.4)	186 (32.1)	103 (16.9)	53 (23.6)	166 (34.9)	96 (15.6)	56 (25.0)	141 (31.6)	80 (14.4)	47 (21.3)	144 (31.9)

The percentage of remission, LDA and HDA are presented in table 5. Most of the patients were in HDA when starting their first b/tsDMARD (82.3%). Most of patients improved already by month 6, with 46.1% being in remission at 6 months. The percentage of remission is stable or even decreasing during time as compared to the 6 months visit. However, the number of patients with available visits with a DAS28 values varies over time.

Table 5. DAS28 response rates over time

	0 months	6 months	12 months	18 months	24 months	30 months	36 months
Remission < 2.6 (n/N, %)	260/2735, 9.5%	1328/2884, 46.1%	773/1760, 43.9%	686/1514, 45.3%	609/1310, 46.5%	616/1286, 47.9%	556/1229, 45.2%
LDA <3.2 (n/N, %)	223/2735, 8.2%	485/2884, 16.8%	292/1760, 16.6%	248/1514, 16.4%	225/1310, 17.2%	224/1286, 17.4%	221/1229, 18.0%
HDA > 3.2 (n/N, %)	2252/2735, 82.3%	1071/2884, 37.1%	695/1760, 39.5%	580/1514, 38.3%	476/1310, 36.3%	446/1286, 34.7%	452/1229, 36.8%

Time to remission is presented in table 6 and figure 1. Overall, the mean time to remission (calculated only among those who reached remission) was 360 days, while median time was 229 days. Stratification by type of treatment, in a Kaplan-Meier curve to account for censoring, showed that patients treated with TNFi as first ever b/tsDMARD reached remission sooner compared to the other treatment groups.

Table 6. Time to remission

Proportion of patients that reach remission (2901/4657) at any time	
Time to first remission	
mean (SD)	359.58 (299.37)
median (IQR)	229 (124-541)

Figure 1. Kaplan-Meier curves of time (days) to remission by type of first b/tsDMARD (TNFi, JAKi, Other).

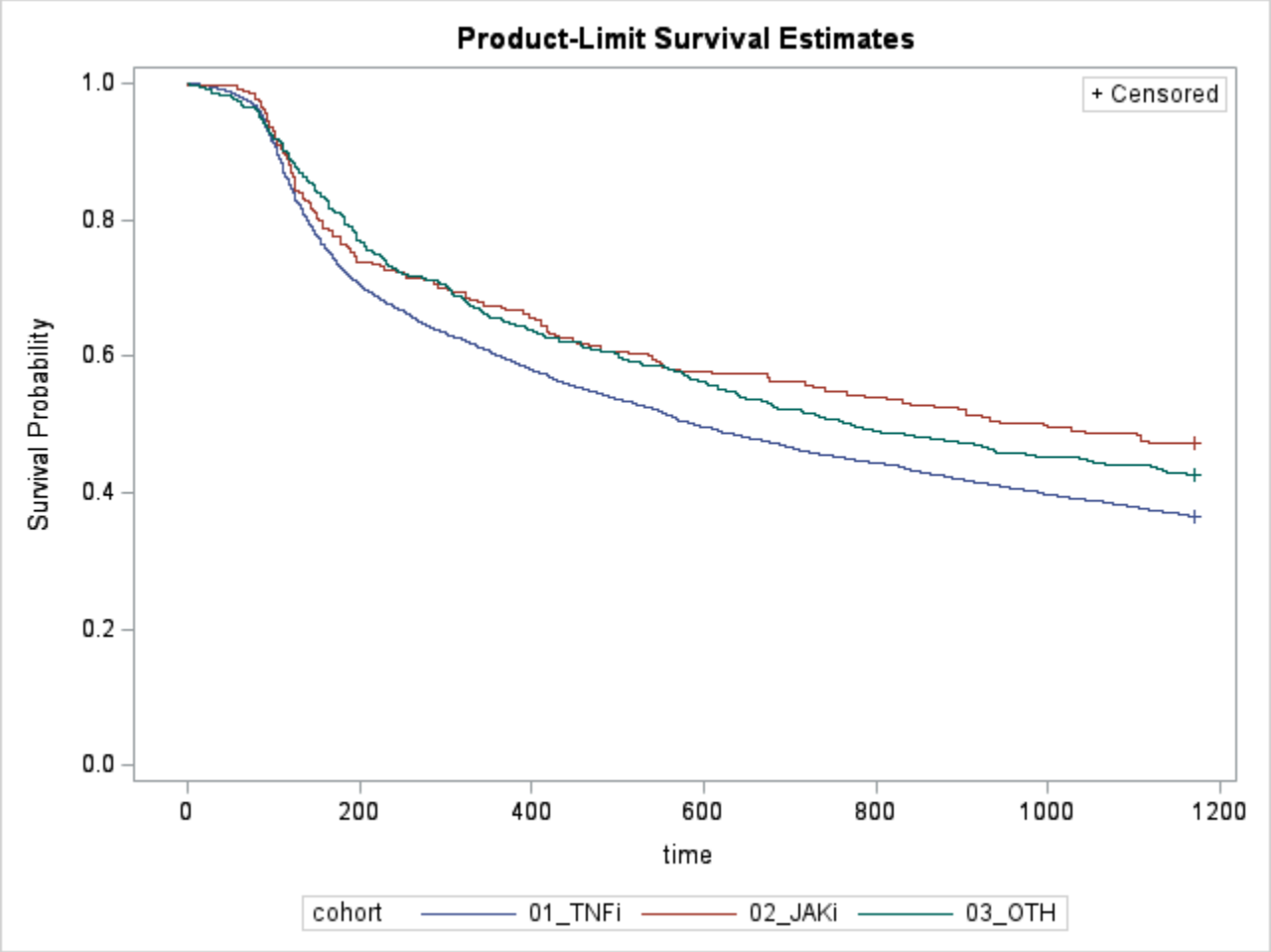


Table 7 present the percentage of patients that switch from the first b/tsDMARD across time, among patients that were not in remission at 3 and 6 months. The percentage of switch was higher among patients that not reached remission at 3 months across all time points. Notably, the differences in percentage between those not in remission at 3 and 6 months was lower by the end of follow-up (only 3.9% difference as compared to the difference at 12 months of 7.2%).

Table 7. Accumulated proportion of patients with a treatment switch over time for patients not in remission 3 (n=2534) and 6 months (n=1219) after treatment initiation.

	Switch at 6 months	Switch at 12 months	Switch at 18 months	Switch at 24 months	Switch at 30 months
Not in remission at 3 months, N(%)	342 (13.5)	636 (25.1)	819 (32.3)	943 (37.2)	1036 (40.9)
Not in remission at 6 months N(%)	216 (17.7)	394 (32.3)	473 (38.8)	513 (42.1)	546 (44.8)

5.0 Discussion

In this retrospective analysis of data from the Swedish Rheumatology Quality Register for patients with RA starting their first b/tsDMARD between 2018 and 2021 we observed a majority of patients starting with a TNFi as their first b/tsDMARD. This is in line with the current national recommendations for RA treatment by the Swedish Society for Rheumatology. (2)

We have previously observed a lower remission rate with increasing age using registry data. (5) The patients starting a JAKi or a non-TNFi-bDMARD as their first treatment were older than the patients starting a TNFi, which could be a negative factor regarding the chance of achieving remission. There were also differences in sex distribution between the treatment groups, with a higher rate of women starting JAKi than non-TNFi bDMARD as the first b/tsDMARD.

When comparing patient groups starting TNFi, JAKi or non-TNFi bDMARD as the first b/tsDMARD differences regarding disease duration, VAS pain, laboratory inflammatory activity and previous treatments were observed. This suggests a selected patient group for each therapeutic strategy. Disease activity as measured by DAS28 was similar between these groups. This indicates a need for treatment options with different modes of action to fulfill the needs of the individual patients.

At 6 months over 45% of the patients had achieved remission independently of treatment regimen. A slightly lower proportion still had DAS28 >3.2. This distribution remained during the following timepoints. In the clinical reality, patients with a well-controlled disease are less eager to visit the clinic and might also not be booked as often for follow up visits. This would lower the proportion of patients in remission among the subjects with a registered DAS28, which could partly explain this finding.

The decreasing number over time of patients with a DAS28 registration emphasizes the challenge of using an index requiring four variables, as DAS28 requires both a patient reported variable, a laboratory variable and variables from a physical examination. If either one is missing, DAS28 cannot be calculated. That also means that patients with a remote visit will not contribute data. Exactly how this might affect the analysis of the different treatment regimens is unclear.

Switching of treatment was common during the follow-up, particularly among patients with HDA and primarilydue to insufficient or declining efficacy. Adverse events are less registered reasons to stop treatment in the later part of the follow-up time for the 1st line. For 2nd and 3rd line the proportion stopping treatment due to lack/loss of efficacy is even more pronounced. The reasons for discontinuation might therefore vary over the treatment periods. Patient with an RA disease refractory to treatment, or difficult to treat RA (D2TRA) would probably be found within this 3rd line group.

Interestingly disease duration was not clearly shorter in patients that achieved remission. A median disease duration of around 2 years might already represent an established disease with any window of opportunity already closed. A higher proportion of ACPA-positivity among patients in remission might however indicate the importance of earlier diagnosis and intensive treatment, as ACPA is a strong indication of RA and might facilitate referral and diagnosis.

The finding that early failure to reach remission (3-6 months) indicates later switch of therapy is interesting and opens for more questions. If more than 40% of the patients who had not reached remission at 3 months have switched therapy at 24 months, but only 14% at 6 months, it is relevant to ask if an earlier switch would give a better outcome in the longer run.

Time to remission was shorter in patients treated with TNFi compared with other treatments. With TNFi being the most recommended treatment after MTX failure, this should be interpreted with caution, as the reasons for not starting a TNFi might be associated with failure to achieve remission, i.e. comorbidity.

6.0 Conclusion

In real world data from SRQ the chance of achieving remission within three years after the start of a first b/tsDMARD is highest in the first months after treatment start and after treatment with a TNFi. The proportion of patients in remission (40-50%) remain over time from 6 months after treatment. Failure to reach remission during the first 6 months of treatment indicates a probability of later switch in more than one out of three patients. Diminishing or insufficient efficacy was the most registered reason for discontinuation of treatment, most prominent for 2nd and 3rd line treatment.

7.0 References

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