USE OF RITUXIMAB COMPARED TO ANTI-TNF AGENTS AS SECOND AND THIRD LINE THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS. A 6-YEAR FOLLOW-UP REPORT FROM THE RHUMADATA® CLINICAL DATABASE AND REGISTRY

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BACKGROUND/PURPOSE

The order of use of biologic agents after failing a TNF inhibitor is still a question for debate. Phase III trial data in TNF-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Prospective registries offer a unique opportunity to observe the effectiveness (combined evaluation of efficacy and safety profile over time) of these agents in a real world clinical setting where all patients with a specific diagnosis and treated in the center are included.

We report here a sixth year follow-up analysis. Our objective is to evaluate if patients with rheumatoid arthritis (RA) treated with rituximab (RIT) after failing a first or a second anti-TNF agents (TNF-IR) have different six -year retention rate than patients similarly prescribed anti-TNF agents (pooled adalimumab, etanercept or infliximab) and compare the treatment strategies of using RIT as second or third biologic treatment.

METHODS

Data from TNF-IR RA patients prescribed adalimumab (ADA), etanercept (ETA), infliximab (INF) or rituximab (RIT) as second or third biologic agents on or after January 1st 2007 was extracted and subjects taking either ADA, ETA or INF were pooled to form the anti-TNF cohort. Baseline data included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluations (VAS), TJC, SJC, CRP and ESR, physician and patient global assessment of disease activity and CDAI. Six-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates. Statistical analysis was performed using SAS version 9.4. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRM and CORQ. All patients with RA are followed over time irrespective of their treatment.

BASELINE CHARACTERISTICS

	Second biologic agent				Third biologic agent			
	Adalimumab n=47	Etanercept n=47	Infliximab n=19	Rituximab n=42	Adalimumab n=13	Etanercept n=8	Infliximab n=11	Rituximab n=44
Age (years)	52.8 (12.8)	57.5 (14.1)	53.0 (15.9)	58.8 (9.7)	56.1 (15.2)	54.1 (12.5)	55.1 (12.1)	56.6 (11.2)
Women, n (%)	32 (68.1%)	38 (80.9%)	12 (63.2%)	31 (73.8%)	12 (92.3%)	06 (75.0%)	09 (81.8%)	35 (79.6%)
Disease Duration (years)	10.3 (6.5)	10.3 (9.5)	6.9 (6.6)	11.7 (9.3)	13.1 (9.3)	13.6 (7.8)	7.1 (5.4)	14.3 (10.1)
Number of secondary diagnoses	1.32 (1.62)	1.28 (1.60)	1.95 (2.25)	1.93 (1.89)	1.32 (1.62)	1.28 (1.60)	1.95 (2.25)	1.93 (1.89)
Number of comorbidities	1.13 (1.39)	1.70 (2.45)	1.58 (2.12)	2.74 (2.91)	1.13 (1.39)	1.70 (2.45)	1.58 (2.12)	2.74 (2.91)
Number of previously used DMARDs	2.7 (1.1)	2.5 (1.1)	2.8 (1.2)	2.8 (0.9)	3.5 (1.2)	2.6 (0.5)	2.8 (1.2)	3.0 (1.3)
Number of concurrently used DMARDs	1.1 (0.7)	0.9 (0.7)	1.2 (0.6)	1.0 (0.7)	0.4 (0.7)	1.1 (0.8)	1.3 (0.6)	1.1 (0.7)
No DMARDs used	*0 (0.0%)*	*1 (2.1%)*	*0 (0.0%)*	*0 (0.0%)*	*9 (69.2%)*	*2 (25.0%)*	*1 (9.1%)*	*7 (15.9%)*
Methotrexate	*31 (66.0%)*	*24 (51.1%)*	*13 (68.4%)*	*26 (61.9%)*	*4 (30.8%)*	*6 (75.0%)*	*8 (72.7%)*	*29 (65.9%)*
Hydroxychloroquine sulfate	*13 (27.7%)*	*15 (31.9%)*	*6 (31.6%)*	*10 (23.8%)*	*1 (7.7%)*	*3 (37.5%)*	*3 (27.3%)*	*14 (31.8%)*
Leflunomide	*4 (8.5%)*	*2 (4.3%)*	*3 (15.8%)*	*4 (9.5%)*	*0 (0.0%)*	*0 (0.0%)*	*2 (18.2%)*	*4 (9.1%)*
Sulfasalazine	*2 (4.3%)*	*1 (2.1%)*	*0 (0.0%)*	*2 (4.8%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (9.1%)*	*2 (4.5%)*
Other	*2 (4.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (2.4%)*	*0 (0.0%)*	*1 (12.5%)*	*0 (0.0%)*	*0 (0.0%)*
Use of corticosteroids	12 (25.5%)	12 (25.5%)	5 (26.3%)	13 (31.0%)	10 (76.9%)	1 (14.3%)	3 (27.3%)	22 (50.0%)
Duration of morning stiffness (minutes)	121.7 (281.6)	72.7 (174.2)	119.7 (366.8)	68.3 (158.6)	28.9 (42.6)	34.9 (20.4)	33.3 (20.7)	104.7 (275.3)
HAQ-DI, range 0-3	1.1 (0.8)	1.2 (0.6)	1.2 (0.8)	1.4 (0.5)	1.4 (1.0)	1.3 (0.7)	1.2 (0.7)	1.5 (0.6)
Fatigue VAS, range 0-10	4.5 (4.0)	4.2 (3.4)	3.9 (3.3)	4.7 (3.1)	4.6 (4.1)	5.8 (3.7)	5.4 (3.5)	5.4 (3.5)
Pain VAS, range 0-10	5.0 (3.5)	4.4 (3.4)	3.9 (2.9)	4.9 (3.1)	4.5 (3.7)	5.9 (2.5)	6.8 (3.4)	5.8 (3.7)
CRP (mg/L)	16.9 (22.2)	6.7 (10.3)	16.7 (31.3)	14.1 (17.7)	6.1 (9.0)	4.4 (2.2)	11.9 (19.2)	19.1 (28.4)
ESR (mm/hr)	26.0 (17.8)	20.7 (16.5)	28.1 (29.2)	28.1 (26.6)	18.5 (15.1)	17.9 (17.0)	25.3 (31.6)	31.7 (31.7)
RF positive (%)	65.9%	65.9%	44.4%	87.5%	50.0%	50.0%	30.0%	88.1%
Anti-CCP positive (%)	64.3%	47.4%	50.0%	84.4%	44.4%	28.6%	40.0%	71.4%
Tender joint count (TJC), range 0-28	5.2 (5.7)	5.5 (5.5)	5.1 (7.2)	6.2 (6.9)	6.6 (5.2)	9.8 (6.6)	8.3 (4.3)	6.8 (6.3)
Swollen joint count (SJC), range 0-28	5.6 (5.3)	6.0 (5.7)	6.7 (8.3)	7.2 (6.0)	7.4 (3.6)	8.2 (6.5)	8.5 (2.1)	8.0 (6.4)
Physician global VAS, range 0-10	3.5 (2.1)	4.2 (1.6)	5.2 (3.5)	4.5 (2.1)	4.6 (3.2)	5.3 (0.7)	5.8 (2.0)	5.1 (2.6)
Patient global VAS, range 0-10	4.4 (3.3)	4.0 (2.8)	3.2 (2.7)	5.0 (2.9)	3.9 (3.4)	6.2 (2.4)	5.8 (3.1)	5.2 (3.4)
Clinical disease activity index (CDAI), range 0-76	17.5 (11.1)	18.5 (13.9)	17.3 (17.0)	19.8 (10.6)	19.0 (11.7)	28.9 (14.9)	26.0 (6.7)	22.1 (11.9)

RESULTS

The data from 231 RA patients were extracted, 155 and 76 having respectively failed a first and a second anti-TNF agent. No clinically significant differences in baseline variables were observed between treatment groups in second and third intention. The principal reasons for biologic cessation were treatment inefficacy, adverse events and other or unspecified reasons. The 6-year retention rates of second line RIT and anti-TNF use were 80.1% and 19.1%, respectively (overall retention difference log-rank p< 0.0001, Figure 1). The overall retention of a second biologic agent was not affected when considering RF+ or anti-CCP+ patients only, Figure 2. In patients having failed two anti-TNF, subsequent use of RIT and anti-TNF agents respectively demonstrated 6-year retention rates of 53.6% and 37.2% (overall retention difference log-rank p=0.0473). Second versus third line use was numerically (80.1% vs 53.6%) and statistically superior (overall retention difference log-rank p=0.0029).

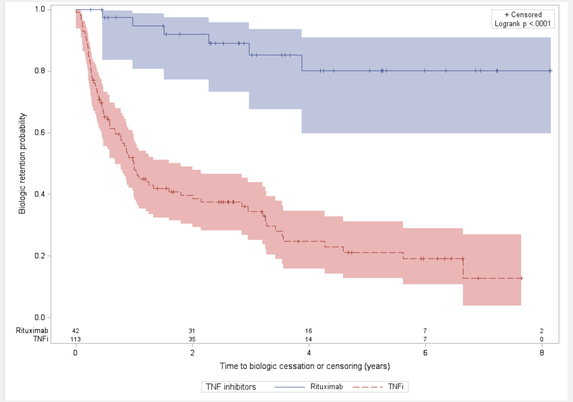

Figure 1. Retention probability of a second biologic agent.

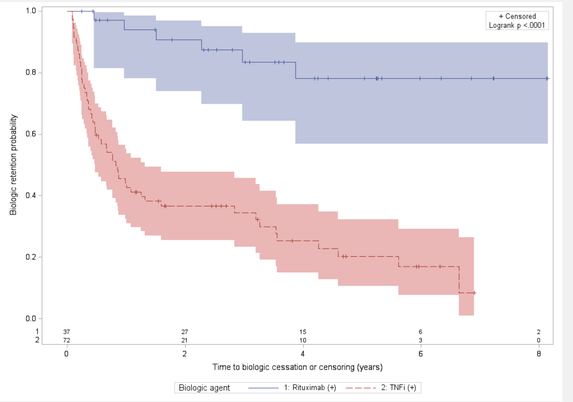

Figure 2. Retention probability of a second biologic agent. Comparing RIT to TNFi among anti-CCP or RF positive patients

CONCLUSIONS

As a second and third line agent, in TNF-IR RA patients, RIT demonstrate better 6-year retention rate than anti-TNF agents. Second line use shows a statistically superior retention rate over third line use. This suggests that using rituximab as a second line therapy after failing a first anti-TF agent is a better strategy than waiting to use it after two different anti-TNF failures. Overall retention of second line biologic agents was not affected when considering RF+ or anti-CCP+ patients only.

Reference: 1. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. Emery P, et al. Ann Rheum Dis 2014 ;0:1–6

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