Is there a downside in off-label use of rituximab? Three-year data from the German biologics register RABBIT.

Adrian Richter[1], Anja Strangfeld[1], Peter Herzer[2], Elke Wilden[3], Arnold Bussmann[4], Joachim Listing[1] and Angela Zink[1,5]

[1]German Rheumatism Research Centre Berlin, [2] Scientific Advisory Board, Munich, [3] Rheumatologist, Cologne, [4] Rheumatologist, Geilenkirchen, [5] Charité University Medicine Berlin

German Rheumatism Research Centre, Epidemiology Unit

EULAR 2013 FRI0212

Background

Rituximab (RTX) is approved in combination with methotrexate (MTX) for the treatment of rheumatoid arthritis (RA) after failure of tumor necrosis factor-α (TNFα) blocking therapy. A substantial number of patients do not tolerate methotrexate and/or other synthetic DMARDs and are treated off-label with RTX in monotherapy or with concomitant leflunomide (LEF).

Objectives

To compare the treatment regimens RTX+MTX, RTX+LEF or RTX monotherapy regarding effectiveness in a 3-year follow-up, taking discontinuation rates, drop-outs and concomitant use of glucocorticoids (GC) into account.

Patients & Methods

We included RTX-naïve patients who started RTX at enrollment in the German biologics register RABBIT between 2007 and 2012 and had a minimum of one follow-up visit (N=907). Therapy discontinuation and drop-out processes were examined in Cox-proportional hazard models. To capture the influence of concomitant use of GC and to compare clinical effectiveness, measured by the disease activity score (DAS28), linear mixed effects models were applied. The issue of missing data and therapy switches was addressed by multiple imputations. To demonstrate the impact of drop-outs and therapy discontinuation we contrasted a completer-analysis (approach 1) versus an intention-to-treat analysis (approach 2).

Conclusions

1. **Regarding effectiveness, off-label use of RTX+LEF or of RTX monotherapy is similar to RTX+MTX therapy.**
2. **RTX+LEF or RTX monotherapy are useful alternatives for patients being intolerant to MTX.**
3. **Our data suggest for rheumatoid factor negative patients to be rather treated with RTX and a concomitant nbDMARD to ensure therapy adherence.**

Results

Patients' baseline characteristics

	RTX+MTX	RTX+LEF	RTXmono
N	496	117	294
Female (n (%))	385 (77.6)	89 (76.1)	233 (79.3)
Age (years, mean (SD))	56.4 (11.7)	57.2 (11.5)	58.8 (12.2)
Disease duration (years, mean (SD))	13.7 (9.9)	13.8 (11.0)	14.7 (10.2)
No. of previous biologics (mean (SD))	1.5 (1.0)	1.6 (0.8)	1.5 (1.0)
Concomitant GC (7.5 – 14mg/d, n (%))	118 (28.0)	19 (20.9)	72 (28.7)
Concomitant GC (> 15mg/d, n (%))	54 (12.8)	12 (13.2)	55 (21.9)
DAS28 (mean (SD))	5.5 (1.2)	5.3 (1.3)	5.7 (1.2)
% of full functional capacity (mean (SD)	55.3 (22.6)	58.4 (22.3)	51.4 (24.1)

TABLE 1: *Baseline characteristics.*

Therapy discontinuation & drop-out

Discontinuation of ITT-therapy was defined as switching to another biologic agent and/or nbDMARD and was significantly higher in patients treated with RTX monotherapy (Fig. 1). Furthermore, patients in RTX monotherapy were more likely to drop out (p<0.001) compared to RTX+MTX. Other predictors of drop-out were being rheumatoid factor negative (p<0.05) or having a higher DAS28 over time (p<0.001).

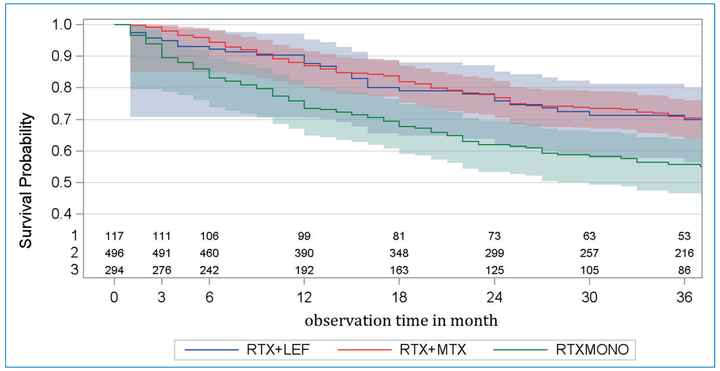

FIGURE 1: *Kaplan-Meier survival curve of therapy discontinuation.*

Concomitant glucocorticoids

The doses of concomitant GC were similar between RTX+MTX and RTX monotherapy. Patients on RTX+LEF therapy received on average 1.6 mg/d less GCs (p≤0.01).

Re-treatment with RTX

There were no significant differences across treatment regimens in time to 1st, 2nd or 3rd re-treatment with RTX (p_{min}> 0.62). In all treatment groups re-treatment with RTX was considered 180 days after the last cycle at the earliest.

Effectiveness

- All approaches were adjusted for patient characteristics assessed at baseline: DAS28, functional capacity, number of comorbidities, previous anti-TNF failures, RF as well as treatment (variable selection according: BIC).
- The completer-analysis (approach 1) indicates a spurious advantage for RTX monotherapy.
- After considering drop-outs and therapy discontinuation in approach 2, no significant differences between treatment regimens were found.
- Significant predictors of disease activity during follow-up were: RF, DAS28 at baseline, number of comorbidities (>2 vs. ≤ 2), and previous anti-TNF failures (> 1 vs. ≤ 1).
- We found no association for: age, sex or weight.

	N	DAS28 at baseline	DAS28 at month 12 [CI]	DAS28 at month 24 [CI]	DAS28 at month 36 [CI]
Completer analysis (approach 1)					
RTX + MTX	216	5.6	3.9 [3.7 – 4.1]	3.8 [3.6 – 4.0]	3.6 [3.4 – 3.9]
RTX + LEF	53	5.6	4.2 [3.8 – 4.6]	4.1 [3.7 – 4.6]	3.7 [3.2 – 4.1]
RTX mono	86	5.6	3.7 [3.5 – 4.0]	3.5 [3.2 – 3.7]	3.4 [3.1 – 3.7]
Intention-to-treat analysis (approach 2)					
RTX + MTX	496	5.5	4.1 [4.0 – 4.2]	3.8 [3.7 – 4.0]	3.7 [3.6 – 3.8]
RTX + LEF	117	5.5	4.1 [3.9 – 4.3]	3.9 [3.7 – 4.2]	3.6 [3.3 – 3.9]
RTX mono	294	5.5	4.0 [3.8 – 4.1]	3.7 [3.5 – 3.8]	3.6 [3.4 – 3.8]

TABLE 2: *Adjusted means estimates of the DAS28 for treatment regimens.*

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

Acknowledgement: We thank all rheumatologists who enrolled at least 40 patients: Kaufmann J, Klopsch T, Krause A, Richter C, Liebhaber A, Bergerhausen H, Tony H, von Hinüber U, Demary W, Gräßler A, Kekow J, Burmester G, Dockhorn R, Eisterhues C, Rockwitz K, Kapelle A, Wassenberg S, Krummel-Lorenz B, Ochs W, Edelmann E, Zinke S, Meier L, Aringer M, Bohl-Bühler M, Remstedt S, Kellner H, Pick D, Stille C, Tremel H, Balzer S, Thiele A, Lebender S, Körber H, Ständer E, Berger S, Weiß K, Krüger K, Karberg K, Sörensen H, Zänker M, Alliger K, Späthling-Mestekemper S, Dexel T, Gause A, Moosig F, Schneider M, Schuch F, Wendler J, Kleinert S, Grebe T, Grünke M, Kühne C, Karger T, Fliedner G, Gauler G, Walter J, Wiesmüller G, Rech J, Krause D, Fricke-Wagner H, Leumann K, Biewer W, Reck A, Menne H, Häntsch J, Schwarze I, Harmuth W, Manger K, Petersen V.

richter@drfz.de