References:

- [1] Esposito AJ, Chu SG, Madan R, Doyle TJ, Dellaripa PF. Thoracic Manifestations of Rheumatoid Arthritis. Clin Chest Med. 2019 Sep;40(3):545-560. doi:10.1016/j.ccm.2019.05.003. Epub 2019 Jul 6. Review. PubMed PMID: 31376890.

Table. Changes in nodule characteristics with respect to treatment groups.

	csDMARD	bDMARDs
SOLID NODULES		
Pre-treatment		
Total number of nodules, n	72	54
Post-treatment		
Completely diminished, n	5	14
Regressed, n	5	12
Stable, n	33	20
Enlarged, n	23	4
Cavitary transformation	6	4
De novo solid nodules	26	7
CAVITARY NODULES		
Pre-treatment		
Total number of nodules	10	16
Post-treatment		
Completely diminished, n	0	1
Regressed	0	5
Stable	4	8
Enlarged, n	6	2
Newly formed cavitary nodules	6	9**

*number less than calculated due to cavitation, **de novo 5 nodules, 4 transformation from solid nodules

Figure. Nodule progression in a patient receiving rituximab (white arrow)

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FRI0110 TAPERING TOWARDS DMARD-FREE REMISSION IN ESTABLISHED RHEUMATOID ARTHRITIS: 2 YEAR RESULTS OF THE TARA TRIAL

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Background: In rheumatoid arthritis (RA) disease outcomes have improved enormously in the last decades. Due to early initiation of therapy, a treat-to-target approach and a growing arsenal of disease-modifying antirheumatic drugs (DMARDs) and biologics, RA patients are in sustained remission more often. This raises the subsequent questions whether treatment should be continued, tapered or stopped. Although DMARD free remission (DFR) is nowadays achievable for increasing numbers of RA patients, the optimal tapering approach still needs to be defined.

Objectives: To evaluate the 2-year clinical effectiveness of two gradual tapering strategies, namely tapering the csDMARD first followed by the TNF-inhibitor, or tapering the TNF-inhibitor first followed by the csDMARD.

Methods: In this multicenter single-blinded randomised controlled trial RA patients with controlled disease for at least 3 consecutive months, defined as a DAS₂₈ ≤ 2.4 and a swollen joint count (SJC) ≤ 1, which was achieved with csDMARDs and a TNF-inhibitor were included. Eligible patients were randomised into gradual tapering csDMARDs followed by the TNF-inhibitor, or vice versa.

Medication was tapered in three steps over the course of 6 months. After 12 months, the other DMARD was tapered. Gradual tapering was done by cutting the dosage into half, a quarter and thereafter it was stopped. In case of a flare (DAS44>2.4 or SJC>1) the previous effective dose was restarted and tapering was not initiated any further throughout the whole study period. The primary outcome for the clinical effectiveness was the number of patients with a disease flare, defined as DAS44>2.4 and/or SJC>1. Secondary outcomes were DFR, disease activity, quality of life and functional ability. Outcomes were calculated in an intention-to-treat analysis, using all available data.

Results: A total of 189 patients were randomly assigned to tapering the csDMARD first or tapering the TNF-inhibitor first. The cumulative flare rate, after 24 months, for tapering the csDMARD first was 61% (95% CI, 50% - 69%) and for tapering the TNF-inhibitor first was 62% (95% CI, 50%-70%) (p=0.35)(figure 1). The cumulative flare rate differed the most between both groups between 12 and 18 months of follow-up (figure 1). Figure 2 shows an overview of how gradual tapering took place and which medication patients were using at different time points(figure 2). This was indicated for both tapering arms, and for the first and second year (figure 2). For the second year, tapering status was only indicated for the patients who actually tapered medication, so who stayed flare-free in the first year. Patients that tapered their csDMARD first were more often able to completely taper their csDMARD (n=30), and subsequently they also had a higher chance of reaching DFR(n=15) (table 1). However, mean DAS and mean HAQ over time and after 2 years did not differ between both tapering arms (table 1).

Table 1. Baseline characteristics and results after 24 months.

	Tapering csDMARD first (n=94)	Tapering TNF-inhibitor first (n=95)
Baseline (T0)		
Age (years), mean (sd)	55.9 (14.1)	57.2 (10.6)
Gender, female, n(%)	66 (71)	58 (61)
Symptom duration (years), median (IQR)	6.0 (4.3-8.5)	6.3 (4.1-8.9)
ACPA positive, n(%)	61 (72)	65 (75)
RF positive, n(%)	49 (57)	56 (64)
2-year follow-up (T24)		
Cumulative flare, n(%)	57 (61)	59 (62)
DMARD free remission, n(%)	15 (16)	8 (8)
Tapered, n(%)	30 (32)	20 (21)
DAS, mean (sd)	1.39 (0.67)	1.30 (0.70)
ΔDAS (T24-T0), mean (sd)	0.41 (0.55)	0.33 (0.77)
HAQ-DI, mean (sd)	0.62 (0.53)	0.52 (0.51)
ΔHAQ-DI (T24-T0), mean (sd)	0.074 (0.40)	0.058 (0.31)

Conclusion: The order in which tapering and stopping medication was performed was not superior to each other based on flare rates, DAS and HAQ. However, patients who tapered their csDMARD first could more often completely taper off their medication and, therefore, also reached DFR more often.

Figure 1 Cumulative flare rate over time. csDMARDs; conventional synthetic disease-modifying antirheumatic drug, TNF-inhibitor; tumor necrosis factor inhibitor.

Figure 2 Overview of gradual tapering per time point.

Numbers indicate percentages of patients. Every 3 months the TNF-inhibitor or csDMARD was tapered until after 6 months the drug could be stopped. In case of a flare, defined as DAS>2.4 and/or SJC>1, patients were set back at their previous effective dose. No further tapering was allowed after having a flare. For the second year (T12 - T24), only tapering status was shown for patients who - according to protocol - should have tapered their medication in the second year. csDMARD; conventional synthetic disease modifying antirheumatic drug.

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FRI0111

TOCILIZUMAB MAY INDUCE SECONDARY HYPOGAMMAGLOBULINAEMIA. A RETROSPECTIVE CASE SERIES OF 42 PATIENTS

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Background: Tocilizumab (TCZ) is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1_k subclass directed against soluble and membrane-bound interleukin 6 receptors (IL-6R) [1].

Interleukin-6 (IL-6) has a pleiotropic effect on inflammation, immune response, and hematopoiesis. When it was first identified, it was named as B-cell-stimulating factor 2 (BSF-2) according to its ability to induce immunoglobulin production in Epstein-Barr virus-transformed B-cell lines or in *Staphylococcus aureus* Cowan 1-stimulated B cells [2-4].

Nowadays, it is known that IL-6 controls the survival, population expansion and maturation of B cells and plasmablasts. In that way, the regulation of Blimp-1 by STAT3 is linked to antibody secretion and is associated with long-lived plasma cells that produce large amounts of immunoglobulin. Furthermore, the ability of IL-6 to promote humoral immunity has been linked to its effects on follicular helper T cells where they promote B cell proliferation and immunoglobulin class switching [5].

Objectives: Hypogammaglobulinaemia is a known complication of some immunosuppressive drugs, not previously described in patients who received therapy with monoclonal antibody against the IL-6R. We aimed to analyze the prevalence of hypogammaglobulinaemia in our series of patients treated with tocilizumab after a carefully diagnostic workup which ruled out other causes and analyzed whether is associated with a higher risk of infection.

Methods: We conducted a retrospective review from 2010 to 2019 of forty-two patients affected with a rheumatic disease and treated with TCZ at our centre. In those patients in whom we had no record of immunoglobulin levels, we determined them in the blood analysis performed by usual clinical practice.

Results: 42 patients were identified, from whom 38 had rheumatoid arthritis. A 31% had immunoglobulin levels prior to starting treatment with TCZ but no one had hypogammaglobulinaemia. 2 patients were excluded due to their underlying disease could justify the IgG level abnormalities. During the treatment's follow-up, we identified that a 30% of the patients (12/40) had hypogammaglobulinaemia. Of those patients in whom immunoglobulin levels had been determined

prior to starting treatment with TCZ, a 36.3% of them (4/11) developed hypogammaglobulinaemia during the follow-up. From the series, we observed a statistical significance tendency ($p=0.0057$) for infection risk in those patients with hypogammaglobulinaemia in contrast to those with normal IgG level (41.5% vs 14.3%, respectively).

Conclusion: Secondary hypogammaglobulinaemia may occurs in patients receiving anti-IL6 agents such as tocilizumab and this could be associated with an increasing infection risk. The prevalence is not precisely known, in part because measurement of IgG prior to or during the treatment has not been a standard of care. No medical data have been previously disclosed about this possible adverse effect of anti-interleukin-6 agents. Nevertheless, ideally randomized trials are needed to assess this initial hypothesis.

References:

- [1] Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B. Tocilizumab (Actemra). Hum Vaccin Immunother. 2017;13(9):1972–1988.
- [2] Tanaka T, Kishimoto T. The biology and medical implications of interleukin-6. Cancer Immunol Res. 2014;2(4):288–294.
- [3] Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10):a016295. Published 2014 Sep 4.
- [4] Kishimoto T. Interleukin-6: discovery of a pleiotropic cytokine. Arthritis Res Ther. 2006;8 Suppl 2(Suppl 2):S2.
- [5] Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease [published correction appears in Nat Immunol. 2017 Oct 18;18(11):1271]. Nat Immunol. 2015;16(5):448–457.

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FRI0112

RISK OF MALIGNANCY WITH NON-TNFI BIOLOGIC OR TOFACITINIB THERAPY IN RHEUMATOID ARTHRITIS: A META-ANALYSIS OF OBSERVATIONAL STUDIES

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Background: With an increasing usage of non-TNFi biologics and tofacitinib, it is crucial to understand the comparative safety of these agents regarding malignancies risk.

Objectives: We aim to assess the risk of developing cancer in patients with RA exposed to non- TNF inhibitors (TNFi) biologics or tofacitinib therapy.

Methods: Systematical search of PubMed, EMBASE and Cochrane Library plus a hand search of conference proceedings were performed for observational studies that reported cancer incidence in patients with RA treated with biologics or tofacitinib with active comparator of conventional DMARDs (csDMARDs) or TNFi. The pooled relative risk (RR) and 95% confidence interval (CI) were calculated with fix-effects or random-effects model.

Results: Of 2,819 identified articles, a total of 10 studies involving over 323,361 patients and 1,179,263 patient-years of follow-up were included. Pooled analysis showed there was no increased risk of developing cancer in general or specific cancer types in RA patients receiving treatment with rituximab (pooled RR 1.13, 95% CI 0.80-1.59), tocilizumab (pooled RR 0.96, 95% CI 0.83-1.11), or tofacitinib (pooled RR 0.97, 95% CI 0.66-1.43), compared with those receiving csDMARDs or TNFi. However, abatacept usage in RA was associated with a slightly increased overall cancer risk (pooled RR 1.13, 95% CI 1.02-1.24) and non-melanoma skin cancer (pooled RR 1.26, 95% CI 1.09-1.45), relative to csDMARDs or TNFi.

Conclusion: Compared with csDMARDs or TNFi, there was no increased risk of malignancies among RA patients treated with non-TNFi biologics or tofacitinib, with exception of abatacept associated with slightly increased total cancer and specific cancer types. Extended researches are required to confirm the findings in a real-world context.

References:

- [1] Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76:960-977.