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.

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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.

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Figure 1. Relative risk of developing cancer between rituximab and csDMARDs. (A) any cancer; (B) all cancer types excluding NMSC; (C) solid tumors; (D) hematological cancer; (E) melanoma; or (F) melanoma. csDMARDs: conventional synthetic disease-modifying antirheumatic drugs. NMSC: non-melanoma skin cancer.

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FRI0113

THE BASELINE SOLUBLE GP130 IS ASSOCIATED WITH THE RESPONSE OF RHEUMATOID ARTHRITIS PATIENTS TO SARILUMAB

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Background: IL-6 contributes significantly to the chronic inflammatory process of rheumatoid arthritis (RA). Sarilumab (SRL), a human anti-human IL-6 receptor alpha monoclonal antibody that blocks the signaling originated by the IL-6/IL-6R complex like tocilizumab, is an effective treatment. However, predictors of the response to sarilumab are still required.

Objectives: We aimed to combine IL-6, soluble IL-6R (sIL-6R) and gp130 (sgp130) levels to identify groups of sarilumab responses.

Methods: This research is a retrospective study. A total of 32 RA patients with SRL therapy in our department from February 1 in 2018 to December 31 in 2019 were included. Serum and clinical data from 32 RA patients were collected before treatment and until the last visit. Follow-up period was up to one year after starting SRL treatment. Serum were tested for IL-6 (Human IL-6 Quantikine ELISA Kit, R&D systems), sIL-6R (Human soluble IL-6R alpha Quantikine ELISA Kit, R&D systems) and sgp130 (Human soluble gp130 Quantikine ELISA Kit, R&D systems), using specific ELISAs according to the manufacturer's instructions. Hierarchical cluster analysis (JMP14.3.0) was used to establish the relationship between IL-6, sIL-6R and sgp130. We evaluated the efficacy of SRL treatment on the last visit using European League Against Rheumatism (EULAR) response criteria in the groups of patients. The other statistical analyses were performed with EZR 1.41, and p Values less than 0.05 were considered significant.

Results: The median age of patients was 70.5 (IQR: 66.5-74.3) years and the median of disease duration was 7.3 (1.7-15.3) years. Nine (28.1%) patients were biologic and Jakinibs naive. The median follow-up periods were 24 (12-26) weeks. The baseline DAS28 was median 4.39 (3.77 - 5.43), and CDAI was 21.1 (11.7-29.5). When comparing responders and non-responders, there were no significant differences in any of the baseline parameters and cytokines. Four statistical significant clusters of RA patients (i.e., Group1, Group2, Group3 and tocilizumab use group before SRL) were defined by serum concentrations of IL-6, sIL-6R and sgp130 at baseline. The levels of IL-6 expressed as median in Group1 patients were 25.6 (14.4-72.2) pg/ml, in Group2 5.9 (3.3-11.3) pg/ml, and in Group3 70.2 (45.4-86.1) pg/ml ($p < 0.002$, significant difference only between Group2 and Group3). The levels of sIL-6R expressed as median in Group1 patients were 38.7 (34.7-45.1) ng/ml, in Group2 35.1 (24.8-41.9) ng/ml, and in Group3 35.7 (34.2-39.8) ng/ml ($p = 0.5477$). The levels of sgp130 expressed as median in Group1 patients were 272.6 (263.0-277.2) ng/ml, in Group2 223.1 (221.0-228.0) ng/ml, and in Group3 204.6 (192.0-207.6) ng/ml ($p < 0.00003$, significant difference between the three groups respectively). There were no significant differences in any of the baseline clinical features and laboratory findings between the three groups. Out of the 8 patients in Group1 had a good or moderate response to SRL. Conversely, the percentage of patients with no response to SRL was higher in Group3 than in Group1 and Group2.

Conclusion: RA patients could be easily stratified prior to the therapeutic intervention with sgp130 related to the IL-6 signal regulation. Group1 patients, who had the best response to SRL, had the highest level of sgp130.

Table 1. Comparison of baseline serum IL-6, sIL-6R and sgp130 of each groups of patients

	TCZ use before SRL	Group 1	Group 2	Group 3	P value
	n=3	N=9	N=8	N=9	
IL-6, pg/mL	69.8, 592.6	Median 25.6 [IQR] [14.4-72.2]	5.9 [3.3-11.3]	70.2 [45.4-86.1]	<0.002 c
sIL-6R, ng/mL	390.5, 481.7	Median 38.7 [IQR] [34.7-45.1]	35.1 [24.8-41.9]	35.7 [34.2-39.8]	0.547
sgp130, ng/mL	205.6, 239.8	Median 273 [IQR] [263-277]	223 [221-228]	205 [192-208]	<0.001 abc

*a, b and c mean that statically significant difference between subgroups as a: group1 vs. 2, b: group 1 vs. 3, c: group 2 vs. 3.

Figure 1. Patients from each group categorized as good, moderate, and no response after sarilumab treatment according to the EULAR criteria

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FRI0114

EFFICACY OF LEVILIMAB, NOVEL MONOCLONAL ANTI-IL-6 RECEPTOR ANTIBODY, IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS: 1-YEAR RESULTS OF PHASE 2 AURORA STUDY

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Background: Previously, 12-week results of phase 2 clinical study of levilimab (LVL) in patients with active rheumatoid arthritis (RA) have been reported¹. The study has met the primary endpoint at W12 confirming that treatment with LVL 162 mg SC + methotrexate (MTX) either QW or Q2W is superior to MTX alone in patients with RA and inadequate response to methotrexate (MTX-IR). Here we report 1-year efficacy and safety data in QW and Q2W arm of the study.

Objectives: This study was aimed to assess the efficacy and safety of 2 dosing regimens of LVL in active MTX-IR RA subjects.

Methods: This multicenter double-blind placebo-controlled study (NCT03455842) enrolled 105 MTX-IR subjects with active RA (ACR2010). The study design is outlined on Figure 1. Secondary endpoints for the open-label period included ACR20/50/70, LDA, remission rates, and DAS28-CRP(4), among others. The safety was evaluated up to W56.

Figure 1. Study design