FRI0101

EFFECTS OF IL6 INHIBITORS ON THE INCIDENCE OF MAJOR ADVERSE CARDIOVASCULAR EVENTS IN RHEUMATOID ARTHRITIS PATIENTS: A SYSTEMATIC REVIEW WITH META ANALYSIS

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Background: Rheumatoid arthritis (RA) is associated with a 2 fold increased risk of cardiovascular events (CVE) and mortality when compared to the general population. The systemic inflammation in RA seems to play a pivotal role by creating endothelial dysfunction and thus accelerating atherosclerosis. This long lasting inflammatory process potentiates the effects of additional classical cardiovascular risk factors. Since the 2000s, numerous therapeutic advances, in particular biologics, allow better control of this inflammation. Among these, IL6 inhibitors (IL6i) are known to provide rapid and sustained improvements in clinical, biological and radiographic outcomes. However, an increase in circulating lipid concentrations in patients treated with IL6i is usual. This raises the question of the risk -to -benefit ratio of IL6i.

Objectives: The purpose of this systematic literature review and meta-analysis was to evaluate the impact of IL6i on the incidence of major adverse cardiovascular events in RA patients in comparison with TNF α inhibitors (TNFi), non TNFi bDMARDs or csDMARDs.

Methods: A systematic literature search of MEDLINE (via PubMed), EMBASE and the Cochrane Library databases until February 2019 was performed. Included studies were observational studies or randomized controlled trials having reported relevant confirmed CVEs (death from CVE, myocardial infarction, heart failure and stroke) in patients with RA treated with IL6i, and a suitable control group. A meta-analysis of the relative risk for each CVE in RA patients treated with IL6i compared to patients in the control groups was performed. A random effect model was applied in case of substantial heterogeneity.

Results: Of 6869 studies, 23 randomized controlled trials and 6 controlled cohorts could be included. IL6i were significantly associated with a reduction in the risk of myocardial infarction in comparison with TNFi (OR, 0.73; 95% CI [0.56 to 0.96]). No other significant effects were observed with regard to the risks of stroke, heart failure (HF), and death from CVE in comparison with csDMARDs, TNFi, or non-TNFi bDMARDs (table 1).

Table 1. Pooled relative risks of cardiovascular events in RA patients treated with IL-6 inhibitors and respective control groups

	Cs DMARDs	TNFi	Non TNFi bDMARDs
Myocardial infarction	1.44 [0.50; 4.17]	0.73 [0.56; 0.96]	0.81 [0.48; 1.36]
Stroke	1.08 [0.40; 2.91]	1.20 [0.82; 1.77]	0.73 [0.39; 1.37]
Heart failure	0.17 [0.01; 4.08]	1.51 [0.61; 3.70]	1.19 [0.71; 1.98]
Cardiovascular death	1.59 [0.62; 4.11]	1.13 [0.72; 1.78]	NA

Our findings of a potentially protective effect of IL6i use on the risk of MI are reassuring. Although several beneficial effects might be involved, like the effective control of systemic inflammation, the anti-arrhythmia effect or the improvement of endothelial and left ventricle dysfunction, a potential indication bias with a decreased likelihood to prescribe these drugs in patients with high cardiovascular risk cannot be excluded.

Conclusion: This review of the literature with meta-analysis provides reassuring results about the association between use of IL6i and CVE in RA patients. Data from long-term observational studies is however needful to confirm and ascertain this result.

Disclosure of Interests: None declared

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FRI0102

SERUM TNFA LEVELS AT 24 HOURS AFTER FIRST ADMINISTRATION OF CERTOLIZUMAB PEGOL PREDICT EFFECTIVENESS AT WEEK 12 IN PATIENTS WITH RHEUMATOID ARTHRITIS FROM TSUBAME STUDY (UMIN ID:0002381)

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Background: To increase the remission rate of rheumatoid arthritis (RA), it is necessary to determine the efficacy of the tumor necrosis factor (TNF) inhibitor as early as possible. Moreover, the response to certolizumab pegol (CZP) at 12 weeks has been reported to predict its long-term efficacy.

Objectives: As part of a prospective single-center observational study (TSUBAME study), we prospectively enrolled patients to be treated with CZP in our institution to evaluate its effectiveness and safety starting at 24 hours after the first dose in clinical settings, while recording blood CZP concentrations and biomarkers over time to examine their correlation with clinical effects.

Methods: One hundred patients with RA and inadequate response to MTX who received CZP were enrolled in the TSUBAME study. The changes in serum TNF α , IL-6, and CZP levels at 24 hours after first administration of CZP were measured, and the correlation between serum biomarkers and clinical response was determined.

Results: At 24 hours after CZP initiation, significant improvement was observed in the disease activity (baseline and 24 h: 5.4 ± 1.3 , 5.0 ± 1.3 , respectively, $p < 0.01$), which was maintained until week 12. (baseline and 12 w: 5.4 ± 1.3 , 3.3 ± 1.4 , respectively, $p < 0.01$). Serum TNF α and IL-6 levels significantly decreased at 24 hours after first administration of CZP compared to baseline. No correlation was found between TNF α and IL-6 levels at baseline and the clinical response. According to univariate analysis, low serum TNF α and IL-6 levels and high CZP levels at 24 hours were associated with DAS28 (ESR) remission at 12 weeks. According to multivariate analysis, low serum TNF α levels at 24 hours were significantly associated with DAS28 (ESR) remission at 12 weeks (OR 0.05, 95%CI 0.01, 0.75, $p = 0.03$). Based on these findings, an ROC curve was created using remission according to the DAS28 (ESR) at week 12 as a dependent variable and TNF α concentration at 24 hours as an independent variable, resulting in a cut-off value of 0.76 pg/ml. From this result, the TNF α concentration at 24 hours was divided into 2 groups according to this cut-off, and the rates of remission according to the DAS28 (ESR) at week 12 were compared. In the group with TNF α concentration at 24 hours below the cut-off value, the rate of remission according to the DAS28 (ESR) at week 12 was significantly higher than in the group with TNF α concentration at 24 hours above the cut-off value (below the cut-off: above the cut-off = 56.3%: 21.6%, $p < 0.001$). Between the group that achieved remission according to the DAS28(ESR) and the group that did not achieve remission at week 12, there was almost no difference in the distribution of TNF α concentrations at baseline; however, the distribution of TNF α concentrations at 24 hours was lower in the group that achieved remission.

Conclusion: CZP was effective where serum TNF α was strongly neutralized within 24 hours. These results suggest that low serum TNF α levels at 24 hours after first administration of CZP may predict the effectiveness of CZP. To increase the remission rate in RA, it is necessary to determine the effectiveness of the molecular targeted drugs used at an early point, in addition to how rapid the onset of action is. CZP is extremely fast-acting, and its effectiveness can be predicted as early as 24 hours after the first dose, suggesting that it may be possible to determine the effectiveness early.

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FRI0103

ASSOCIATION BETWEEN SEROPOSITIVITY AND DISCONTINUATION OF INFLIXIMAB IN RHEUMATOID ARTHRITIS

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Background: Infliximab is still a widely used biologic agent in treatment of rheumatoid arthritis (RA). Because infliximab is expensive and can have adverse events, identification of factors that predict an adequate response to this treatment has been investigated.

Objectives: In this study, we investigated the association between rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) status and

the discontinuation of infliximab therapy due to adverse events or insufficient response in bio-naïve patients with RA.

Methods: This study included patients enrolled in the Tsurumi Biologic Communication Registry in Japan. A crude comparison of infliximab discontinuation between seropositive and seronegative patients was using Kaplan-Meier analysis and log-rank test. We evaluated the associations between the specified baseline characteristics and discontinuation of infliximab therapy using Cox proportional hazard regression. We could not perform simultaneous assessments of the impact of RF and ACPA seropositivity on clinical efficacy because of collinearity.

Results: Baseline characteristics of the patients included in this study are shown in Table 1 and the crude comparison between RF and ACPA status is shown in Figure 1. RF and ACPA seropositivity was significantly predictive of discontinuation of infliximab therapy after adjusting for baseline characteristics, including age, sex, stage, class, disease activity at baseline, and prednisolone use (Table 2). The hazard ratio was 1.99 (95% confidence interval 1.25, 3.18) for RF and 2.73 (95% confidence interval 1.24, 6.02) for ACPA.

Table 1. Characteristics of RA patients at baseline by RF and ACPA status

	RF (n = 344; 985 patient-years)			ACPA (n = 250; 824 patient-years)		
	RF		P†	ACPA		P†
	positive (n = 263)	negative (n = 81)		positive (n = 211)	negative (n = 39)	
Age, years (SD)	55.7 (12.3)	54.6 (13.9)	0.48	55.4 (12.3)	49.7 (14.3)	0.01
Female, no. (%)	205 (78.2)	66 (81.5)	0.64	170 (80.6)	28 (71.8)	0.28
DAS28ESR (SD)	5.50 (1.33)	4.95 (1.51)	0.005	5.54 (1.28)	4.61 (1.82)	0.0005
Stage I+II/III+IV, no. (%)	81/174 (31.8/68.2)	25/50 (33.3/66.7)	0.78	61/139 (30.5/69.5)	15/20 (42.9/57.1)	0.17
Class I+II/III+IV, no. (%)	155/102 (60.3/39.7)	52/22 (70.3/29.7)	0.14	126/72 (63.6/36.4)	23/12 (65.7/34.3)	0.85
Current MTX treatment, %	100	100	1	100	100	1
MTX dose, mg/ week (SD) ‡	7.56 (2.16)	7.80 (2.22)	0.4	7.82 (2.20)	7.31 (2.66)	0.22
Current PSL treatment, no. (%)	141 (68.1)	37 (56.1)	0.077	128 (67.4)	19 (55.9)	0.24
PSL dose, mg/day (SD) ‡	3.98 (3.91)	2.70 (2.74)	0.01	3.73 (3.78)	2.63 (2.85)	0.11
BMI, kg/m ² (SD)	22.6 (3.88)	21.3 (4.22)	0.1	22.0 (4.10)	22.5 (3.33)	0.68

Data are presented as mean, unless otherwise stated. SD: standard deviation

† Chi-square test for categorical variables and t-test for continuous variables.

‡ MTX dose and PSL dose were mean value in patients with concomitant MTX and PSL treatment, respectively.

Table 2. Cox proportional hazard regression for infliximab therapy due to adverse event and insufficient response

Model including RF status (n = 226)			Model including ACPA status (n = 182)		
Variable	HR (95% CI)	P	Variable	HR (95% CI)	P
RF positive	1.99 (1.25-3.18)	0.0037	ACPA positive	2.73 (1.24-6.02)	0.012
Age at baseline	0.99 (0.98-1.01)	0.43	Age at baseline	0.99 (0.98-1.01)	0.36
Sex (referent: male)	1.21 (0.76-1.94)	0.41	Sex (referent: male)	0.99 (0.60-1.62)	0.96
Prednisolone use	1.03 (0.71-1.49)	0.85	Prednisolone use	1.02 (0.67-1.56)	0.92
Stage III + IV (referent: I + II)	1.01 (0.99-1.03)	0.17	Stage III + IV (referent: I + II)	1.01 (0.98-1.03)	0.54
Class III + IV (referent: I + II)	0.99 (0.98-1.02)	0.73	Class III + IV (referent: I + II)	0.99 (0.97-1.01)	0.55
DAS28ESR at baseline	0.95 (0.83-1.10)	0.54	DAS28ESR at baseline	0.99 (0.84-1.18)	0.97

Conclusion: RF and ACPA seropositivity in bio-naïve patients with RA correlated with a higher rate of infliximab discontinuation due to adverse events or ineffectiveness.

Disclosure of Interests:

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Fig. 1 Kaplan-Meier survival curve and log-rank test.

(a) Discontinuation of infliximab therapy, stratified by RF status. (b) Discontinuation of infliximab therapy, stratified by ACPA status.

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FRI0104

PERSISTENCE OF TOCILIZUMAB THERAPY AMONG PATIENTS WITH RHEUMATOID ARTHRITIS: DATA FROM THE US-BASED CORRONA RHEUMATOID ARTHRITIS REGISTRY

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Background: Understanding the persistence of biologic therapies and factors associated with discontinuation can help inform treatment decisions for patients with rheumatoid arthritis (RA).

Objectives: To evaluate the persistence of tocilizumab (TCZ) therapy and identify factors associated with its discontinuation among US patients with RA in routine clinical practice.

Methods: Eligible participants were TCZ-naïve patients enrolled in the Corrona RA registry who initiated TCZ after January 1, 2010 and had ≥ 1 follow-up visit. Persistence of therapy was defined as maintaining continuous TCZ treatment with no interruptions; patients were considered no longer persistent upon the first discontinuation of TCZ. Persistence was calculated using Kaplan-Meier survival analysis for the overall population; secondary analyses evaluated persistence excluding patients who stopped TCZ with no reported reason for discontinuation (patients with non-medical reasons for discontinuation [eg, insurance] were censored) and in only those patients who initiated intravenous (IV) TCZ. Cox proportional hazards modeling was used to identify factors associated with persistence.

Results: A total of 1789 TCZ initiators were included; 81.0% were female, 85.0% were white and 75.4% were overweight or obese. The mean (SD) age was 58.5 (12.6) years and mean (SD) disease duration was 12.0 (9.6) years. Most patients (93.4%) had prior biologic use and 67.4% had received ≥ 2 prior biologics. Overall, 28.8% initiated TCZ as monotherapy. Among all TCZ initiators, the median (95% CI) duration of persistence was 20 (18 to 22) months (Fig 1). Factors associated with an increased hazard of TCZ discontinuation included smoking and higher baseline CDAI, whereas prior tumor necrosis factor inhibitor (TNFi) use was associated with a reduced hazard (Fig 2A). After excluding patients with no reported reason for discontinuation (remaining n = 1303), the median (95% CI) duration of persistence was 46 (38 to 55) months (Fig 1); smoking, use of 1 prior non-TNFi and higher baseline patient pain score were associated with an increased hazard of discontinuation (Fig 2B). Among the 1284 patients who initiated TCZ IV, median (95% CI) duration of persistence was 22 (19 to 25) months (Fig 1); smoking, lack of insurance and higher baseline patient fatigue score were associated with an increased hazard of discontinuation, whereas use of 1 prior TNFi was associated with a decreased hazard (Fig 2C).

Conclusion: In this real-world population of US patients with RA, TCZ was most frequently initiated after an inadequate response to ≥ 2 biologics. Overall median duration of persistence was approximately 20 months and was higher (46 months) when patients with no reported reason for TCZ discontinuation were excluded. As expected, factors indicative of higher baseline disease activity were associated with shorter persistence.