POS0461

RESPONSE TO BIOLOGIC THERAPY IN RHEUMATOID ARTHRITIS: RETHINKING OUR CLASSIFICATION

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Background: In rheumatoid arthritis (RA), primary failure with biologic treatment may be understood as lack of initial clinical response, while secondary failure would be loss of effectiveness after an initial response. Despite these clinical concepts, there is no unifying operational definition of primary and secondary non-response to RA treatment in observational studies using real-world data. On top of data-driven challenges, when conceptualizing secondary non-responders, it is unclear if the mechanism behind loss of effectiveness after a brief initial response is similar to loss of effectiveness after previous benefit sustained over time.

Objectives: This viewpoint aims to motivate discussion on how to define primary and secondary non-response in observational studies. Ultimately, we aim to trigger expert committees to develop standard terminology for these concepts.

Methods: We discuss different methodologies for defining primary and secondary non-response in observational studies. To do so, we shortly overview challenges characteristic of performing observational studies in real-world data, and subsequently, we conceptualize whether treatment response should be a dichotomous classification (Primary response/non-response; Secondary response/non-response), or whether one should consider three response categories (Primary response/non-response; Primary sustained/non-sustained response; Secondary response/non-response).

Results: RA or biologic registries are a common data source for studying treatment response in real-world data. While registries include disease-specific variables to assess disease progression, missing data, loss of follow-up, and visits restricted to the year or mid-year visit may present a challenge. We believe there is a general agreement to assess primary response within the first 6 months of treatment. However, conceptualizing secondary non-response, one could wonder if a patient with brief initial response and immediate loss of it should belong to the same response category as a patient who relapses after a period of prior benefit that was sustained over time. Until this concern is clarified, we recommend considering a period of sustained response as a pre-requisite for secondary failure. This would result in the following three categories: a) Primary non-response: Lack of response within the first 6 months of treatment; b) Primary sustained response: Maintenance of a positive effectiveness outcome for at least the first 12 months since treatment start; c) Secondary non-response: Loss of effectiveness after achieved primary sustained response. Figure 1 illustrates this classification through a decision tree. Since the underlying mechanisms for treatment failure may differ among the above-mentioned categories, we recommend to use the three-category classification. However, since this may pose additional methodological challenges in real-world data, optionally, a dichotomous 12-month time-point may be used to assess secondary non-response (unfavourable outcome after 12-months) in comparison to primary non-response or non-sustained response (unfavourable outcome within the first 12-months). Similarly, to study primary response, the solely 6-month timepoint may be used.

Figure 1. Decision tree to classify treatment response to biologics in rheumatoid arthritis (RA) based on evidence of an initial response, assuming a sustained benefit as pre-requisite prior secondary non-response. Patients discontinuing treatment due to remission or safety reasons are not reflected in the decision tree.

Conclusion: A unified operational definition of treatment response will minimize heterogeneity among observational studies and help improve the ability to draw cross-study comparisons, which we believe would be of particular interest when identifying predictors of treatment failure. Thus, we hope to open the room for discussion and encourage expert committees to work towards a common approach to assess treatment primary and secondary non-response in RA in observational studies.

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ALCOHOL AND INFLAMMATORY ARTHRITIS DISEASE ACTIVITY: PERSPECTIVES FROM A 979-PATIENT COHORT WITH SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The effect of alcohol on disease activity in inflammatory arthritis remains poorly understood. Studies of alcohol and the incidence or risk of inflammatory arthritis are conflicting [1,2]. Alcohol does downregulate pro-inflammatory cytokines and may therefore reduce immune-mediated disease activity.

Objectives: This study investigates the relationship between alcohol consumption and disease activity in our inflammatory arthritis patient cohort and performs a systematic review with meta-analysis.

Methods: Cohort Study Design and data analysis

Patients attending a rheumatology clinic between 2010-2020 were prospectively followed. Information on demographics, alcohol use, smoking habits, and disease outcome measures were collected. Statistical analysis included univariate and multivariate linear and binary logistic regressions, Mann Whitney-U tests, and one-way ANOVA with Tukey's HSD.

Meta-analysis

EMBASE, Pubmed, the Cochrane library, and Web of Science were searched. Studies reporting on alcohol consumption and disease activity in a cohort of RA patients were included for further investigation. Forest plots were generated from 95% confidence intervals of extracted data using mean differences. Linear regression was used to determine correlations between alcohol and antibody status, gender, and smoking status.

Results: Cohort Study

Of the 979 analysed patients, 62% had RA, 26.7% had PsA, and 11.2% had AS. Mean DAS28-CRP in RA and PsA at one year was 2.96 ± 1.39 , and 64.2% of patients were in remission ($\text{DAS28-CRP} \leq 2.6$ or $\text{BASDAI} \leq 4$). Both male gender and risky drinking (>15 units of weekly alcohol) were both significantly associated with remission. Compared to women, men had an odds ratio of 1.78 [1.04, 2.52] ($p=0.034$) for any alcohol consumption and 6.9 [4.7, 9.1] ($p=0.001$) for drinking at least 15 weekly drinks. when adjusted for gender, there was no significant association between alcohol and disease activity. Yet, when adjusted for alcohol consumption, gender still influenced disease activity.

Meta-analysis

The search identified 4126 citations of which 14 were included. The pooled mean difference in DAS28 (95% CI) was 0.34 (0.24,0.44) ($p<10^{-5}$) between non-drinkers and drinkers, 0.33 (0.05,0.62) ($p=0.02$) between non-drinkers and heavy drinkers, and 0 (-0.3,0.3) ($p=0.98$). between low- and high-risk drinkers. There was a significant difference in the mean difference of HAQ assessments between those who drink alcohol compared to those who do not (0.3 (0.18,0.41), $p<10^{-5}$). There was no significant correlation between drinking and gender, smoking status, or antibody positivity.

Conclusion: While it appears that alcohol is linked to remission in inflammatory arthritis, this association is lost when adjusted for gender. Men with inflammatory arthritis drink significantly more than women and men generally have less severe disease activity. However, the meta-analysis suggests alcohol consumption is associated with lower disease activity and self-reported health assessment in rheumatoid arthritis.

Figure 1. Mean differences in DAS28 between drinking groups. A between non-drinkers and drinkers. B between non-drinkers and high-risk drinkers. C between low-risk and high-risk drinkers.

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POS0463

BEST CARDIOVASCULAR RISK CALCULATOR TO PREDICT ABNORMALITIES IN LEFT VENTRICULAR GEOMETRY IN RHEUMATOID ARTHRITIS

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Background: A relationship between rheumatoid arthritis (RA) and the presence of abnormalities in left ventricular (LV) geometry such as eccentric remodeling has recently been determined, even in the absence of cardiovascular risk factors and before clinical manifestations (1). The 2016 European League Against Rheumatism (EULAR) recommendations that cardiovascular (CV) risk prediction models should be adapted by a 1.5 multiplication factor in RA patients. Risk prediction algorithms based on the CV risk factors (CVRF) have been an important tool for adopting preventive measures and intensifying therapies based on the estimated risk but their application in predicting cardiac structural abnormalities has never been studied.

Objectives: The aim of the study is to determine the CV risk calculator that best predicts alterations in ventricular geometry in RA.

Methods: A cross-sectional, observational study of 108 RA patients between 40-75 years (ACR / EULAR 2010 classification criteria). The QRISK3, OMNI-BUS, Framingham Risk Score Lipids (FRSL), Framingham Risk Score BMI (FRS-BMI) and Reynolds Risk Score (RRS) calculators were compared. The diagnostic performance was determined by ROC curves, and the discriminative capacity by the Area Under the Curve (AUC) 95% CI. The echocardiogram was the diagnostic gold standard. A p value < 0.05 was considered statistically significant.

Results: The prevalence of abnormalities in ventricular geometry was 38.9%. QRISK3 reported AUC of 0.656, 95% CI (0.550-0.762, $p=0.006$), cut-off point ≥ 4.6 , sensitivity of 73.8% and specificity of 54.5%, and likelihood ratio of +1.62. FRS-BMI showed AUC of 0.653, 95% CI (0.543-0.762, $p=0.008$), cut-off point ≥ 11.02 , sensitivity and specificity of 61.9% and 57.6% respectively, and likelihood ratio of +1.46. OMNI-BUS showed AUC of 0.635, CI 95% (0.525-0.746, $p=0.018$), cut-off point ≥ 3.8 , sensitivity and specificity of 57.1% and 68.2%. While RRS had AUC 0.644, 95% CI (0.534-0.755, $p=0.012$), cut-off point of 2.25, sensitivity of 47.6% and specificity 78.8%, and likelihood ratio of +2.24 (Figure 1 and Table 1).

Table 1. Discriminatory capacity of the different cardiovascular risk calculators.

Calculators (cut-off point).	AUC	CI 95%		p	Sensitivity	Specificity
		Inferior	Superior			
QRISK (≥ 4.60)	0.646	0.537	0.754	0.012	73.8%	54.5%
SCORE	0.591	0.475	0.706	NS	-	-
OMNI-BUS (≥ 3.80)	0.621	0.509	0.734	0.038	57.1%	68.2%
FRSL	0.594	0.480	0.707	NS	-	-
FRS-BMI (≥ 11.02)	0.642	0.530	0.754	0.015	61.9%	57.6%
RRS (≥ 2.25)	0.627	0.514	0.741	0.029	47.6%	78.8%

Figure 1. ROC curves of the different cardiovascular risk calculators.

Conclusion: The QRISK3 calculator showed the highest discriminative ability and sensitivity to predict abnormalities in LV geometry. However, all calculators demonstrated the need for a lower cut-off point to predict alterations in ventricular geometry. Our findings require adequate reproducibility in other population groups to determine the applicability of CV risk algorithms as predictors of structural alteration of LV.

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IS IT POSSIBLE TO IDENTIFY INDIVIDUALS AT IMMINENT-RISK OF SUB-CLINICAL JOINT INVOLVEMENT?

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Background: In anti-CCP antibody (Ab) positive at-risk individuals with MSK symptoms but without clinical synovitis, the detection of ultrasound (US) sub-clinical inflammation is associated with an increased risk of progression to inflammatory arthritis (IA) ¹. Studies suggest that in these at-risk individuals, MSK symptoms develop before subclinical joint inflammation occurs on US. As such, anti-CCP Ab positive individuals with MSK symptoms in the absence of clinical or sub-clinical inflammation may be at the critical time-point for preventive treatments, before joint inflammation occurs and eventually becomes established (i.e., before the 'second-hit' in RA pathogenesis); however, identifying these individuals is challenging.

Objectives: To identify, in second generation anti-CCP Ab (CCP2+) at-risk individuals with MSK symptoms, but without clinical or sub-clinical synovitis, predictors of US sub-clinical synovitis.

Methods: In 186 CCP2+ at-risk individuals with normal baseline US scan (i.e., no synovitis or bone erosions), and a complete dataset, US data were analyzed at 6, 12 months, then annually until occurrence of IA. US synovitis was identified according to the EULAR/OMERACT definitions². Relevant demographic (age and gender), clinical [early morning stiffness (EMS), tenderness in the small joints of the hands] and serological [anti-CCP2 Ab level, third generation anti-CCP Ab