

EULAR 2022 Highlights

Predictors, outcomes and prognosis in RA

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DISCLOSURES

- Speaker honoraria & participation in advisory boards for Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, Lilly, Fresenius.
- Recipient of research grants from Pfizer and Lilly.
- Member of EULAR TF on D2T RA.
- British Medical Association Doris Hillier Grant Award 2018 – focus on clinical aspects, including multimorbidity in RA.
- FOREUM ECR grant 2021 – focus on bio & non-bio predictors of outcomes in RA.

CRITERIA FOR SELECTION

- High-rating scientific abstracts
- EMEUNET Do Not Miss selection
- Congress 'Highlights' sessions
- WIN & HOT sessions
- Personal selection



RA PREDICTORS

DISEASE ASSESSMENT

EARLY DISEASE DETECTION

ROLE OF IMAGING

Identifying patients who will develop RA among those presenting with UA represents a clinical dilemma.

Discordance between clinical disease activity and imaging is well-recognised and may lead to under/overtreatment.

Can we reliably identify patients with UA who will develop RA?

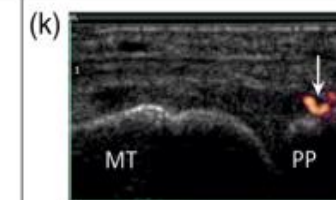
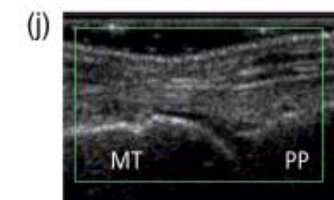
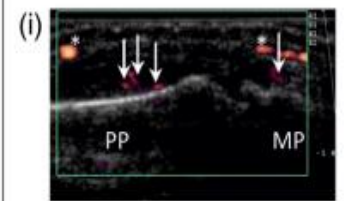
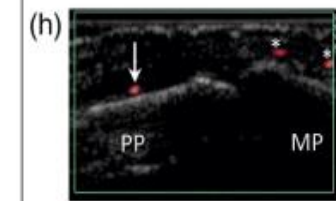
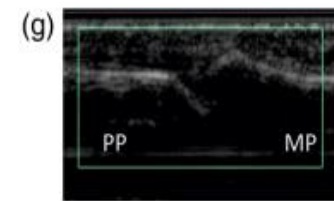
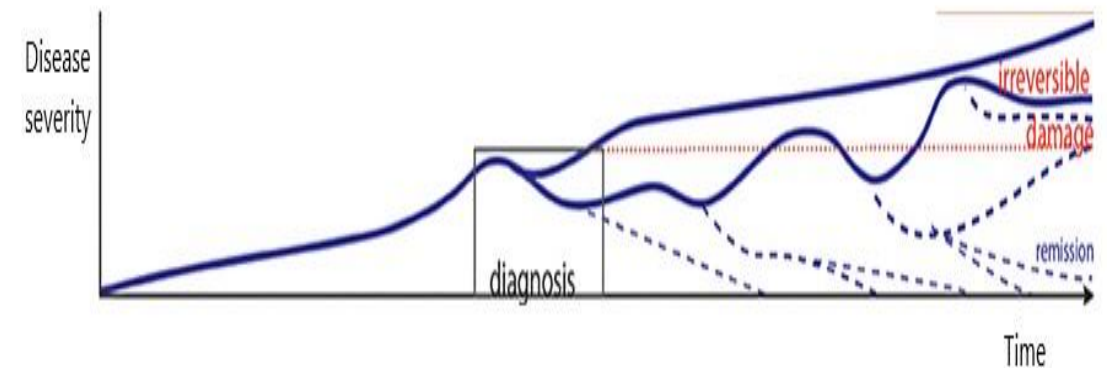
Which factors affect clinical and radiological discordance & can early treatment influence this?

WHAT IS KNOWN & QUESTIONS?

RHEUMATOID ARTHRITIS: A HETEROGENEOUS DISEASE!

❖ RA: different disease trajectories and outcomes

- Ultrasound (US) is increasingly used to supplement disease activity measures e.g. DAS28, SDAI, CDAI.
- US demonstrates phenotypic variation at the level of the joint complex.
- Joint level involvement may extend to extracapsular involvement.



DISCORDANCE BETWEEN DAS28 AND PDUS IN RHEUMATOID ARTHRITIS

- Presence of PDUS is well-documented across different definitions of clinical remission – often referred to as ‘remission discordant’.
 - 34% in Boolean remission²
 - 21% in DAS28 remission¹
 - 19% in SDAI remission¹
- Conversely, absence of PDUS has been reported with raised disease activity measures - referred to in some studies as ‘active discordant’.³
- An early RA study³ documented 25% remission discordance and 22-34% active discordance after 12 months of treatment.

DISCORDANCE BETWEEN DAS28ESR AND PRESENCE OF ULTRASOUND POWER DOPPLER DURING EARLY TREATMENT IS ASSOCIATED WITH DISTINCT CLINICAL AND IMAGING PHENOTYPES AT PRESENTATION

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❖ Study objective

- To identify pre-treatment clinical factors associated with discordance and change in DAS28-PDUS status during early treatment in an early RA trial cohort.

❖ Methods

- 'VEDERA' trial; 120 treatment-naïve, new RA patients randomised to either
 - 1st line ETA+MTX or
 - MTX-treat-to-target regime, escalation to ETN+MTX if not in DAS28ESR remission at week 24.
- Clinical & MSUS assessments at 0, 12, 24 & 48 weeks.

❖ Main findings

- DAS28ESR & PDUS discordance & concordance have **distinct clinical & imaging phenotypes at presentation.**
- Approximately a third transition from AC at baseline to AD early on with treatment.
- A sizeable proportion of AD persist in the face of disease-modifying treatment.
- **Early treatment with ETN+MTX increases probability of clinical and imaging remission as early as week 12.**
- Presence of PDTS at baseline is a good prognostic factor for DAS28 remission with/without PDUS.

❖ Clinical relevance?

- Value of MSUS.
- Understanding the basis for these phenotypes is helpful to facilitate optimal intensive treatment and/or alternative management strategies.

AC = DAS28ESR > 2.6 & PDUS > 0
 AD = DAS28ESR > 2.6 & PDUS = 0
 RC = DAS28ESR ≤ 2.6 & PDUS = 0
 RD = DAS28ESR ≤ 2.6 & PDUS > 0

Change in discordance/concordance over time

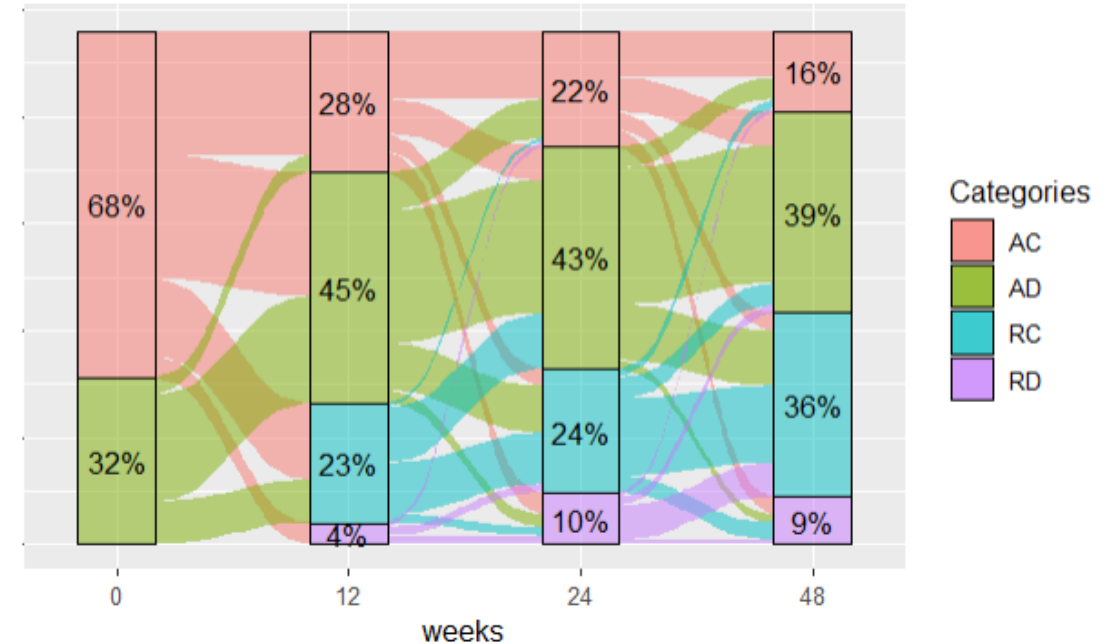


Figure 1: Proportion in different discordant/concordant groups from baseline to week 48. AC: active concordance, AD: active discordance, RC: remission concordance, RD: remission discordance.

OP0083 (2022)

HAND AND FOOT MRI IN CONTEMPORARY UNDIFFERENTIATED ARTHRITIS: IN WHICH PATIENTS IS MRI VALUABLE TO DETECT RHEUMATOID ARTHRITIS EARLY? – A LARGE PROSPECTIVE STUDY

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❖ **Study Objective**

- To study the predictive value of MRI for progression to RA in UA.

❖ **Methods**

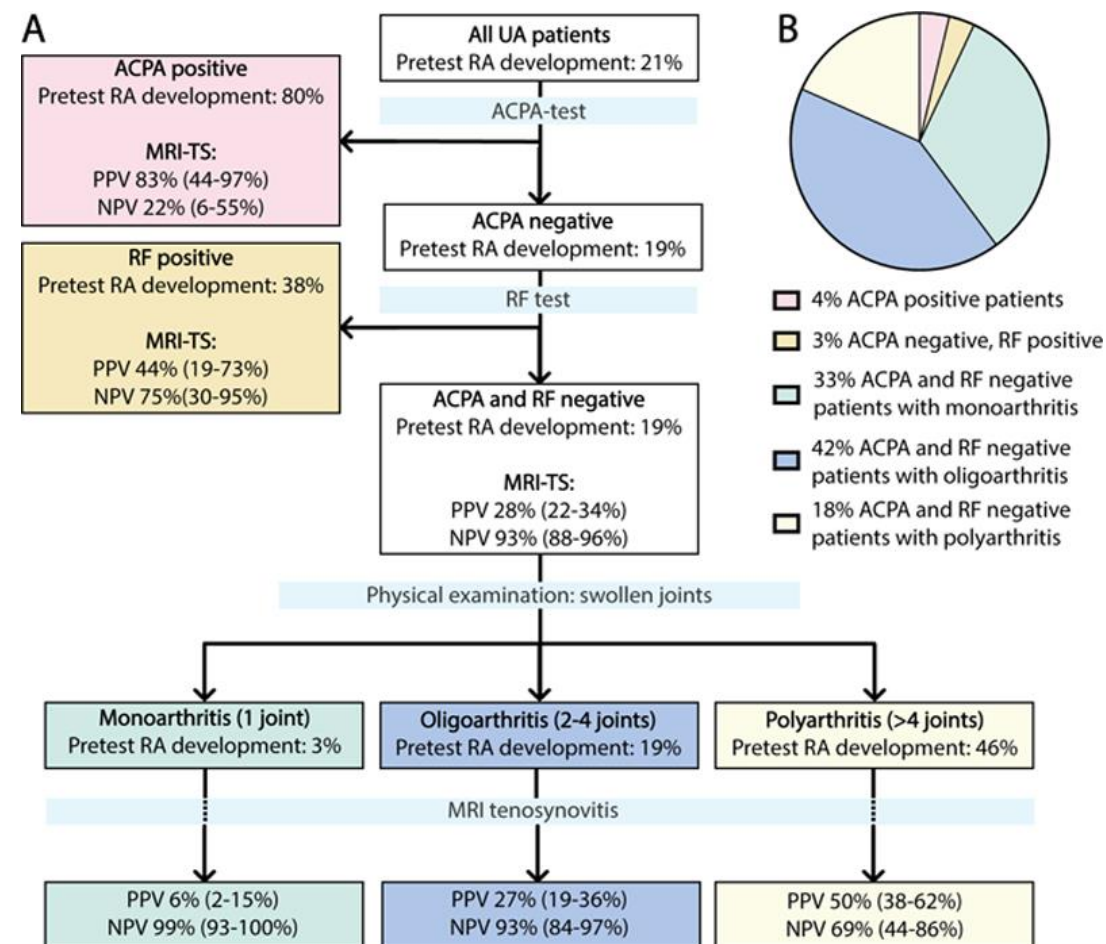
- Two UA-populations were studied: criteria-based-UA (n=405) and expert-opinion-based-UA(n=564), i.e. UA indicated by treating rheumatologists.
- Patients retrieved from a large cohort of consecutively included early arthritis patients undergoing contrast-enhanced MRI-scans of hand and foot at baseline.
- Patients followed for RA-development during 1-year.
- Test-characteristics of MRI were determined separately for subgroups based on joint-involvement and autoantibody-status.

❖ Main findings

- Among criteria-based-UA patients (n=405), 21% developed RA.
- MRI-detected synovitis and tenosynovitis were predictive.**
- MRI-detected tenosynovitis was independently associated with RA-progression (OR 2.79; 95%CI 1.40-5.58), especially within ACPA-negative UA-patients (OR 2.91; 1.42-5.96).**
- Prior risks of RA-development for UA-patients with mono-/oligo-/polyarthritis (3%, 19%, 46%, respectively) were changed by MRI-results mostly for the oligoarthritis-subgroup: PPV was 27% and NPV 93%. Similar results were found in expert-opinion-based-UA (n=564).

❖ Clinical relevance?

- MRI is a valuable means for detecting synovitis and tenosynovitis in ACPA-negative UA-patients with oligoarthritis. A negative MRI could help prevent overtreatment.



INTERVENTION WITH METHOTREXATE IN ARTHRALGIA AT RISK FOR RHEUMATOID ARTHRITIS TO REDUCE THE DEVELOPMENT OF PERSISTENT ARTHRITIS AND ITS DISEASE BURDEN (TREAT EARLIER): A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED TRIAL

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Methotrexate modified the disease course as measured by sustained improvement in MRI-detected inflammation, related symptoms and impairments



RA OUTCOMES

ROLE OF GENES

ROLE OF ANTIBODIES

RA is a heterogeneous disease with patients exhibiting variable susceptibility to structural damage.

Genetic variations within the HLA-DRB1 gene have been consistently associated with both susceptibility and radiographic outcome in RA.

How and which non-HLA markers associated with radiographic outcomes?

What is the role of auto-antibodies?

WHAT IS KNOWN & **QUESTIONS?**

STRATIFIED MEDICINE: GENETIC PREDICTORS OF RADIOGRAPHIC OUTCOME IN RHEUMATOID ARTHRITIS

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⁵The University of Manchester, Lydia Becker Institute of Immunology and Inflammation, Faculty of Biology, Medicine and Health, Manchester, United Kingdom

❖ Study Objectives

- Identify all single nucleotide polymorphisms (SNPs) outside the HLA that have ever been associated with radiographic outcome in RA
- To perform a replication study to determine which of these are associated with radiographic outcome in a large prospective cohort.

❖ Methods

- SNPs identified from the literature through a systematic review, were extracted and tested for an association with the presence of erosions (as a longitudinal binary variable) using a generalized estimating equation (GEE) model in NOAR (large primary care-based inception cohort of patients diagnosed with inflammatory polyarthritis).

❖ Main findings

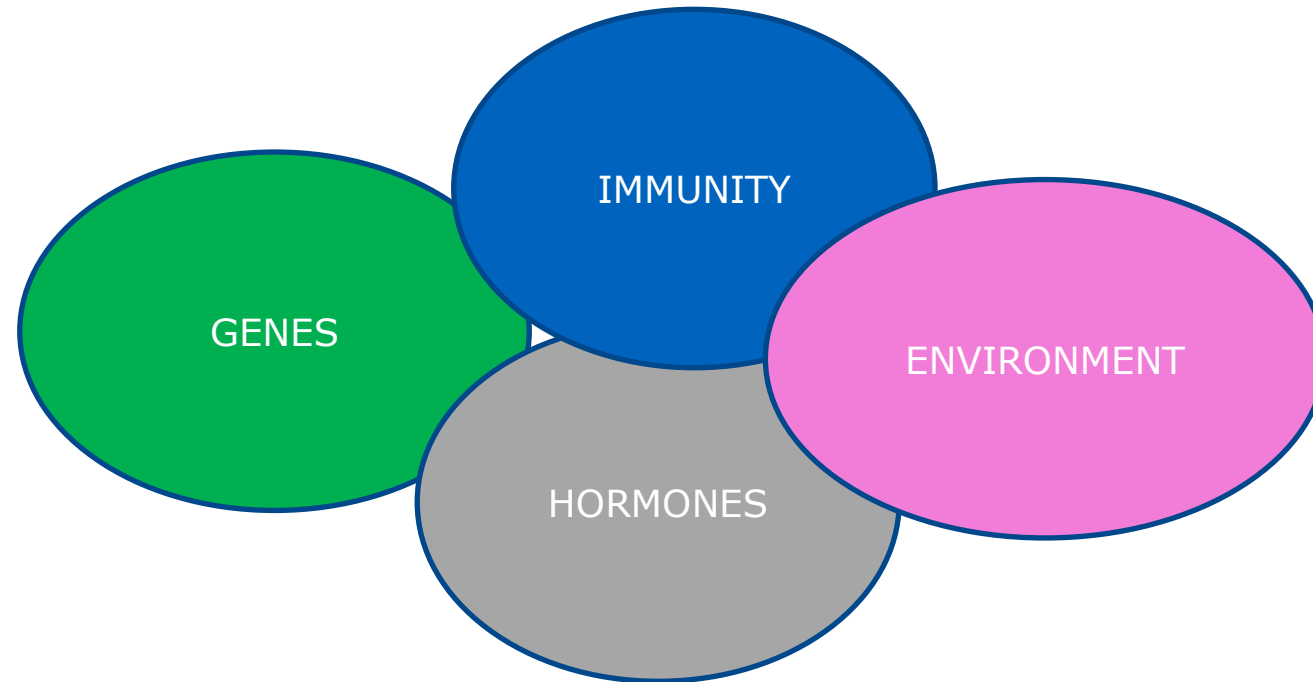
- A total of **113 different non-HLA SNPs associated with radiographic outcome in RA** were identified from the literature. Of these, 102 were successfully identified within NOAR.
- **14 SNPs were found to be significantly associated with the presence of erosions within NOAR.**

| Gene | Chromosome | SNP (single nucleotide polymorphism) | Odds ratio (95% CI) | P value |
|--------|------------|--------------------------------------|---------------------|---------|
| IL2RB | 2 | rs743777 | 1.23 (1.01, 1.05) | 0.0398 |
| IL15 | 4 | rs6821171 | 0.82 (0.67, 1.00) | 0.0451 |
| IL4 | 5 | rs2243250 | 1.36 (1.08, 1.70) | 0.0094 |
| FOXO3 | 6 | rs12212067 | 0.75 (0.58, 0.97) | 0.0278 |
| OPG | 8 | rs2073618 | 0.79 (0.64, 0.98) | 0.0295 |
| TRAF1 | 9 | rs10760130 | 1.33 (1.06, 1.65) | 0.0118 |
| TRAF1 | 9 | rs10818488 | 1.32 (1.06, 1.64) | 0.0141 |
| TRAF1 | 9 | rs2900180 | 1.32 (1.07, 1.61) | 0.0079 |
| IL4r | 16 | rs1805010 | 1.25 (1.01, 1.56) | 0.0393 |
| IL4r | 16 | rs1805011 | 1.31 (1.03, 1.66) | 0.0260 |
| LGALS9 | 17 | rs3763959 | 1.28 (1.03, 1.59) | 0.0260 |
| SOST | 17 | rs4792909 | 1.34 (1.09, 1.65) | 0.0052 |
| LILRA3 | 19 | rs103294 | 0.80 (0.65, 0.98) | 0.0334 |
| MMP9 | 20 | rs11908352 | 0.70 (0.57, 0.85) | 0.0005 |

❖ Clinical relevance?

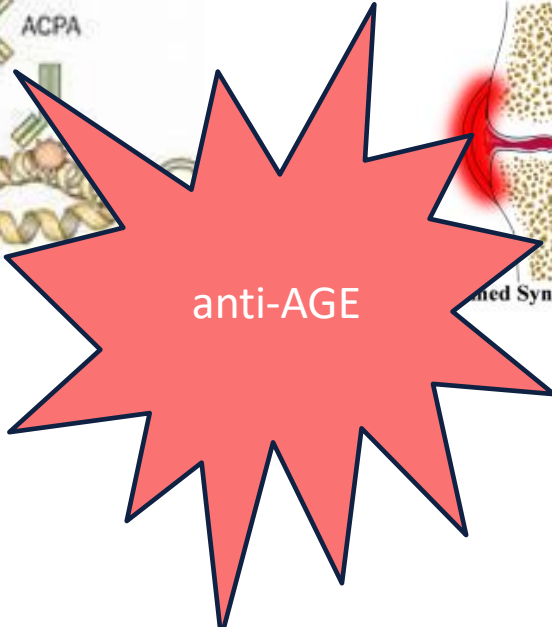
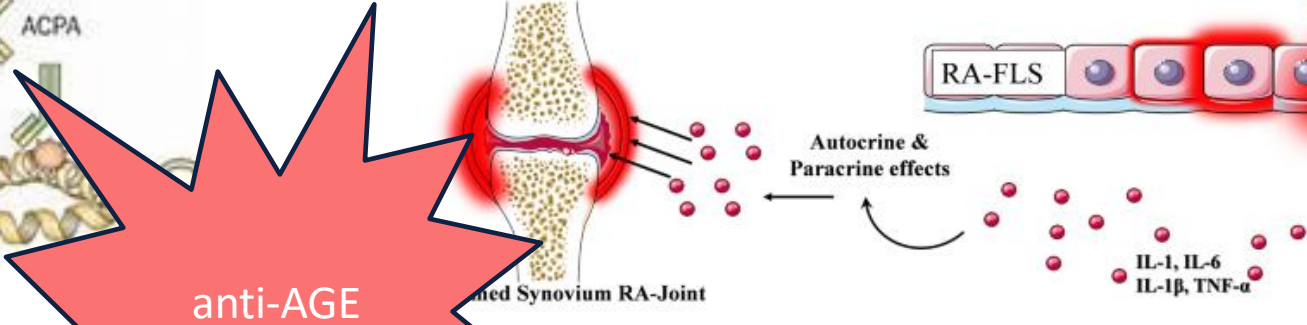
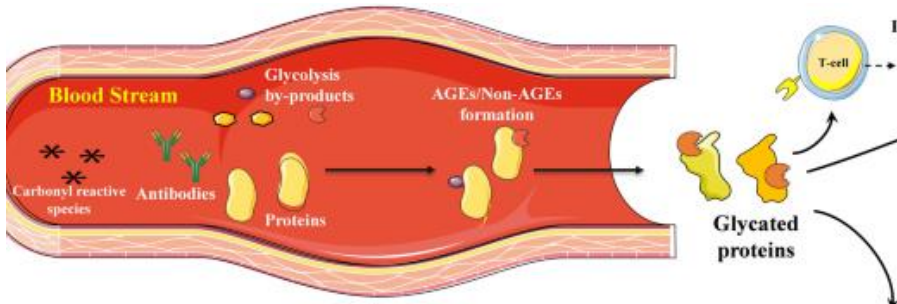
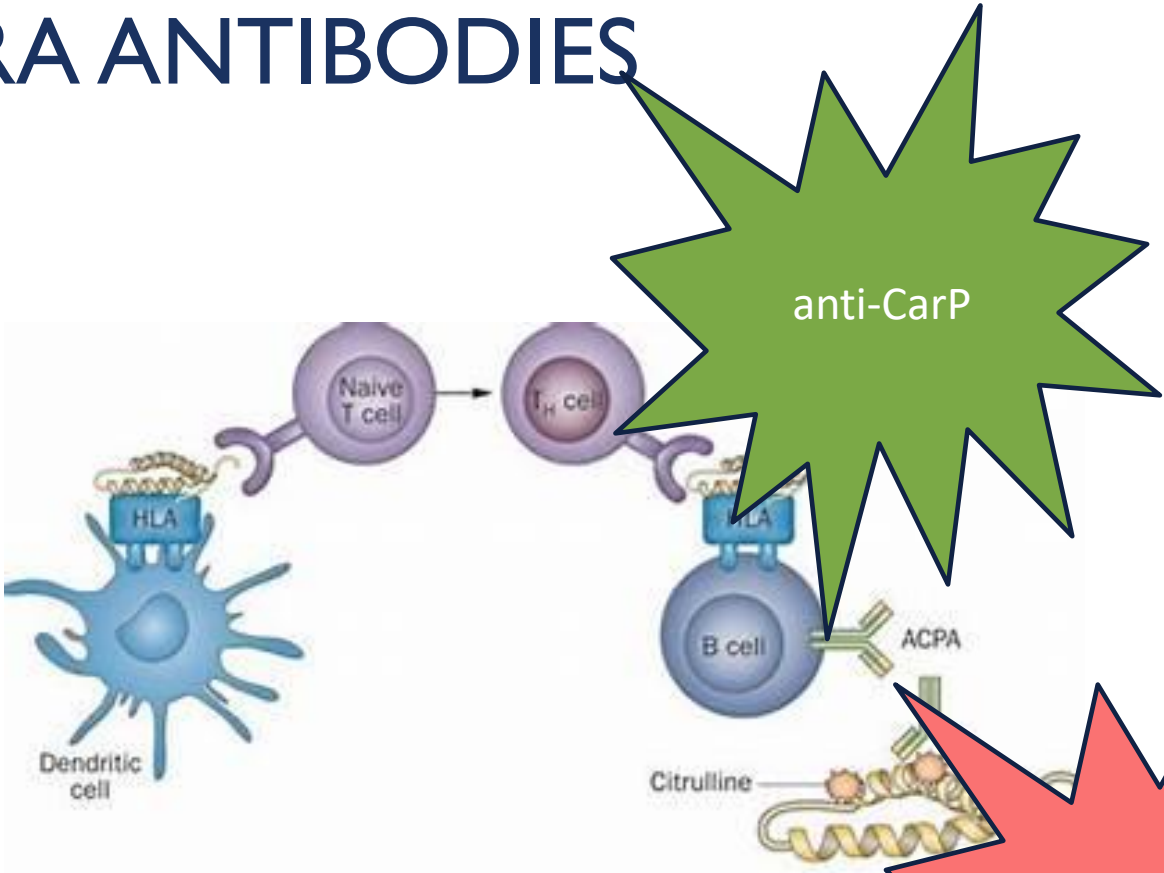
- Genetic analysis may provide insight into potential causal mechanisms of disease severity to identify therapeutic targets and help us stratify patients in the future.
- Added clinical value in predicting radiographic outcomes when combined with clinical/serological/demographic markers.

'Mosaic autoimmunity'



Shoenfeld and Isenberg, Immunol Today, 1989

RA ANTIBODIES



Willemze et al., Nat Rev Rheumatol 2012

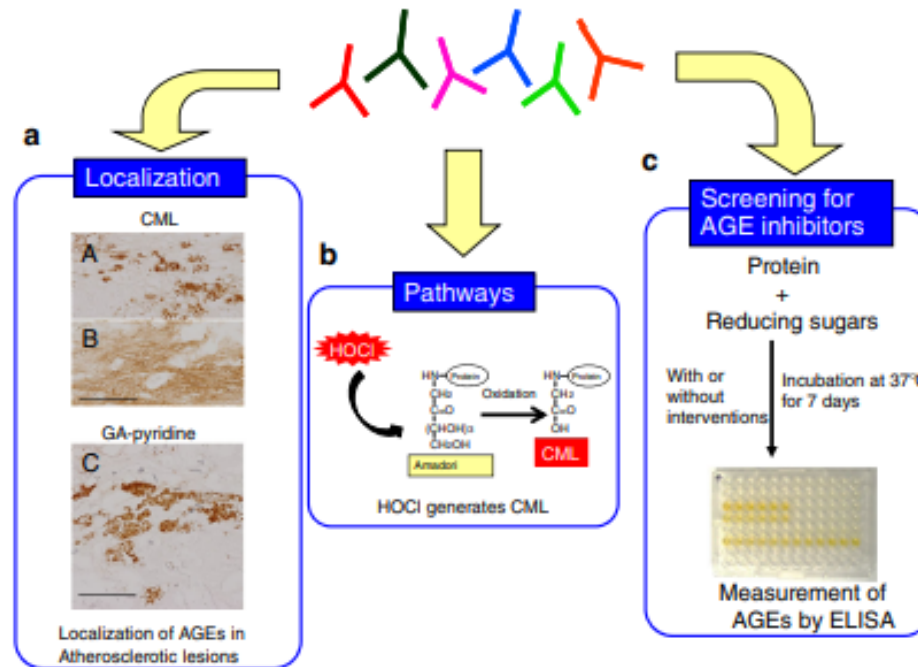
Monu et al., Inflammation 2022

ANTI-AGE

Directed against advanced glycation end-product (AGE) modified proteins.

Anti-AGE have been described in multiple diseases including diabetes, and hypertension.

AGEs are a marker of oxidative stress.



ANTIBODIES AGAINST ADVANCED GLYCATION END-PRODUCTS (ANTI-AGE) DISTINGUISH PATIENTS WITH A MORE INFLAMMATORY PROFILE AND WORSE OUTCOME IN SERONEGATIVE RHEUMATOID ARTHRITIS

T. J. van **Wesemael**¹, M. D. van den Beukel², A. T. W. Hoogslag¹, T. Huizinga¹, R. Toes¹, L. A. Trouw², D. van der Woude¹

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❖ Study Objective

- To investigate the prevalence of anti-AGE in RA and non-RA arthritis patients, as well as their association with clinical parameters and disease outcome in RA.

❖ Methods

- Patients from the Leiden Early Arthritis Clinic (648 RA patients and 538 non-RA).
- IgG antibody levels were measured using an in-house fetal calf serum (FCS) ELISA based assay using native FCS as control.
- Radiological progression measured with the Sharp van der Heijde score (SHS) on yearly basis and the association with anti-AGE was assessed with a multivariate normal regression model.

❖ Main findings

- Almost half of the RA patients are anti-AGE positive **including a substantial part of otherwise completely seronegative RA patients.**
- Anti-AGE antibodies are **associated with inflammatory parameters and radiologic progression in seronegative RA patients.**

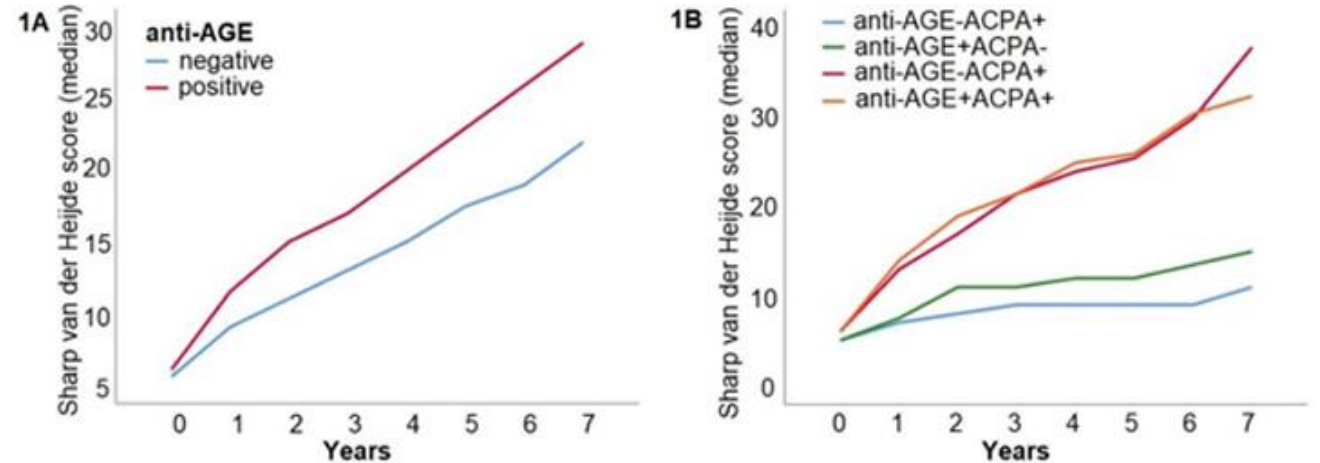


Figure 1. Erosion scores according to the presence of autoantibodies. Figure 1A: Median erosions scores assessed by Sharp van der Heijde method (SHS) during the disease course stratified for anti-advanced glycation end-products antibodies (anti-AGE). A significant difference was found between anti-AGE-negative patients and anti-AGE-positive patients ($B=1.05$, $p<0.001$). Figure 1B: Median erosions scores assessed by SHS during the disease course stratified for anti-AGE and anti-citrullinated protein antibodies (ACPA). SHS was significantly higher in all autoantibody-positive groups compared to the anti-AGE-ACPA- group.

❖ Clinical relevance?

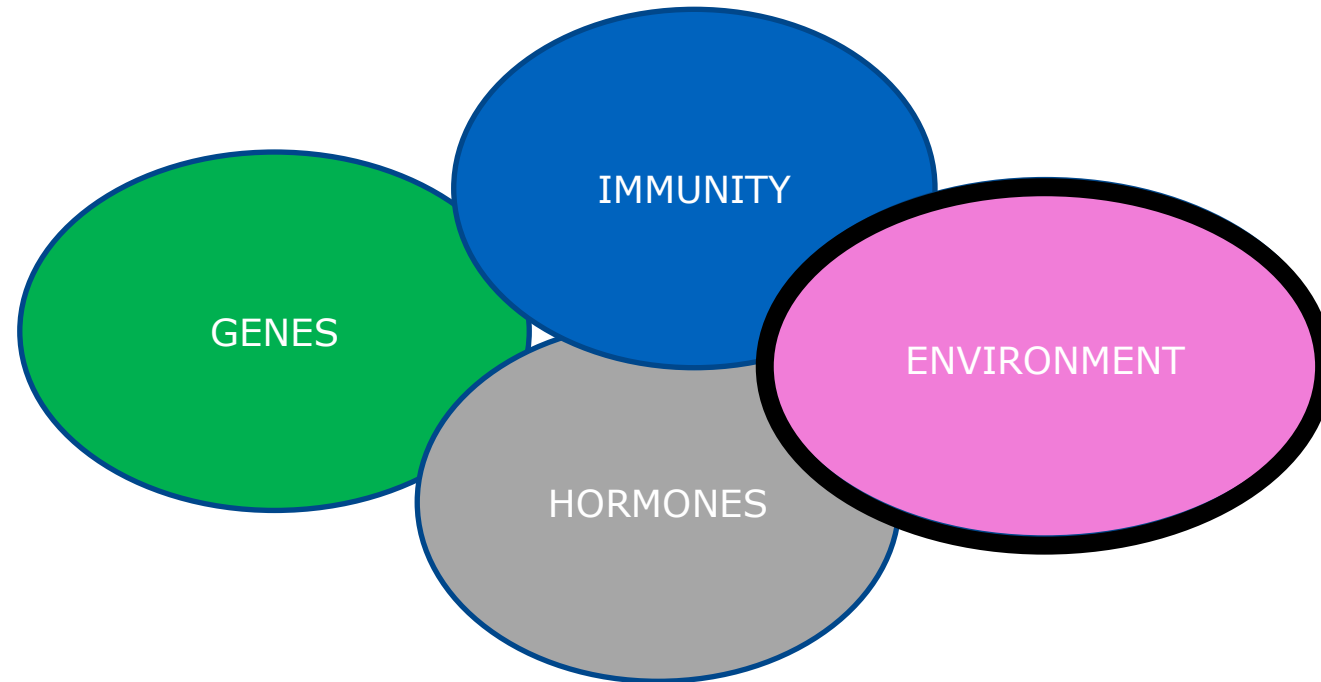
- Although not specific for RA, anti-AGE could potentially identify patients with a more inflammatory phenotype and more severe disease outcome in “classic” autoantibody-negative RA patients.



OUTCOMES & PROGNOSIS I

THINKING BEYOND BIOLOGICAL
FACTORS

'Mosaic autoimmunity'



Shoenfeld and Isenberg, Immunol Today, 1989

Ample evidence on the role of biological (clinical) factors on disease progression & outcomes.

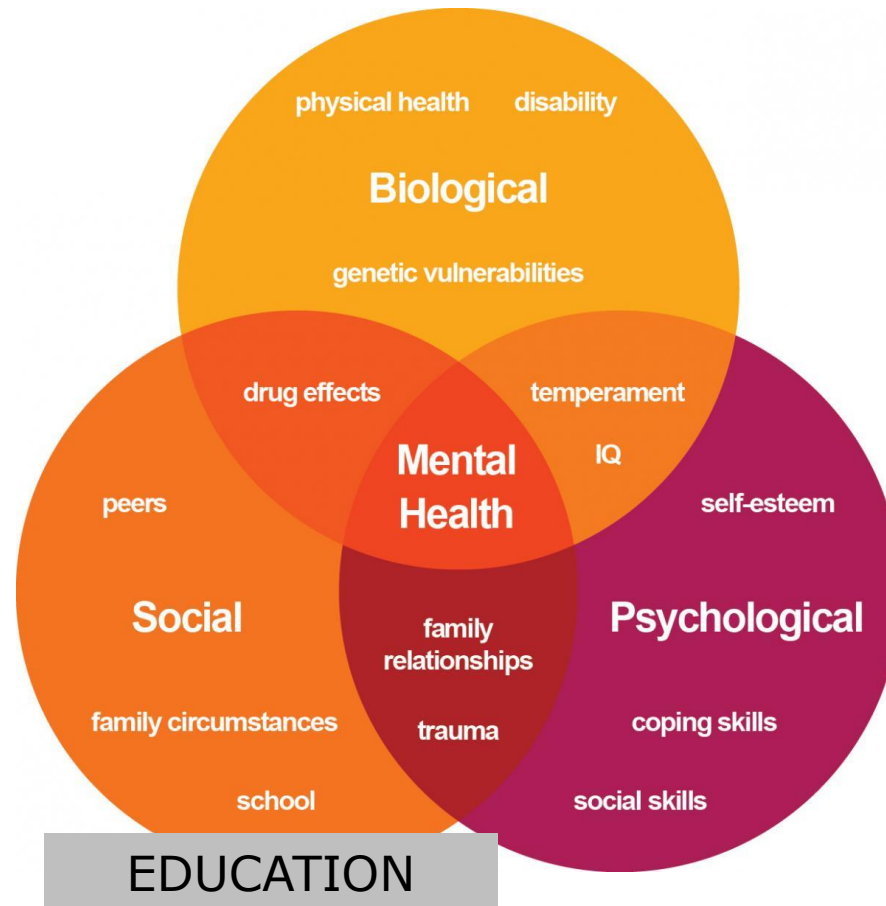
Accumulating evidence on the role of SE factors.

Which SE factors impact disease outcomes & how?

How do SE factors & biological factors interplay to drive disease in RA?

WHAT IS KNOWN & **QUESTIONS?**

'Bio-psychosocial' models in disease



CLINICALLY SUSPECT ARTHRALGIA PATIENTS WITH A LOW LEVEL OF EDUCATIONAL ATTAINMENT HAVE AN INCREASED RISK TO DEVELOP INFLAMMATORY ARTHRITIS

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²Erasmus Medical Centre, Rheumatology, Rotterdam, Netherlands

❖ Study objective

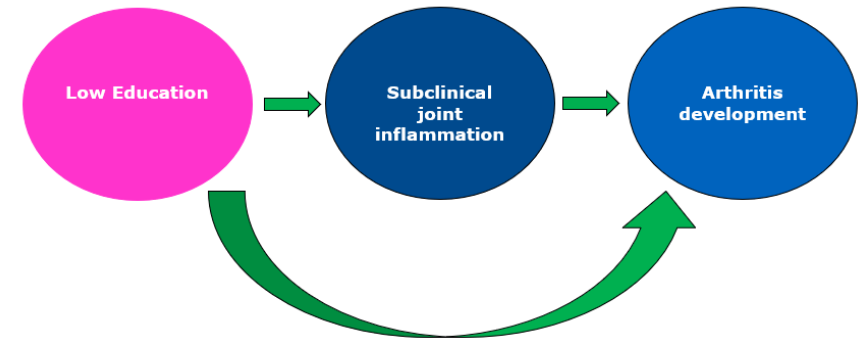
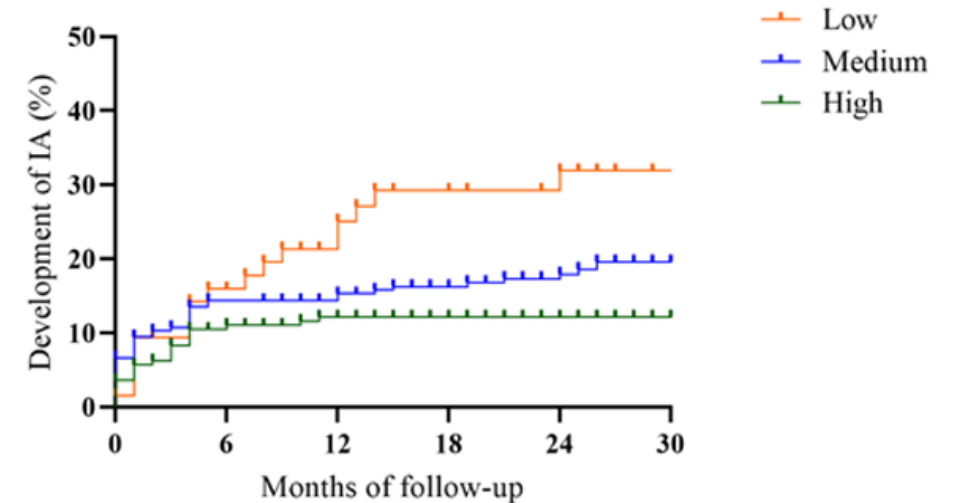
- To determine the association between educational attainment and progression from clinically suspect arthralgia to IA and to perform mediation analysis to elucidate pathways.

❖ Methods

- 600 consecutive patients presenting with clinically suspect arthralgia were followed for the development of IA, identified at joint examination by rheumatologists during median follow-up of 25 months
- Association between educational attainment and IA-development was studied with cox-regression analysis. To evaluate if subclinical joint inflammation is intermediary in the path of educational attainment and IA-development, a three-step mediation analysis was performed, before and after correction for age.

❖ Main findings

- **Low educational attainment was associated with increased IA-development** (HR=2.5, 95%CI=1.4-4.7, $p=0.003$), also after correction for age, BMI and smoking-status (HR=2.1, 95%CI=1.03-4.4, $p=0.041$).
- Patients with a **lower educational level had higher levels of subclinical inflammation at presentation**, which associated with higher risk of progression to IA.
- Mediation analyses: the **association between low educational attainment and IA-development reduced when adding the level of subclinical inflammation**, suggesting that the association between educational attainment and IA-development is partly mediated by higher levels of subclinical inflammation.



❖ Clinical relevance?


- Lower educational attainment of patients with arthralgia is associated with a higher risk of developing arthritis, partly caused by more severe subclinical joint inflammation.
- Study highlights the relevance of SE factors during the development of RA.

'HOT' EULAR SESSION: DIFFICULT TO TREAT RA

Professor Jacob van Laar



D2T RA: contributing factors

| | Univariable OR (95%CI, p-value) | Multivariable OR (95%CI, p-value) |
|--|---------------------------------|-----------------------------------|
| Higher age of onset | 0.97 (0.95-0.996, 0.02) | 0.98 (0.95-1.00, 0.05) |
| Female gender | 0.95 (0.45-2.01, 0.89) | 1.04 (0.46-2.34, 0.92) |
| RF positivity | 1.62 (0.76-3.42, 0.21) | 1.47 (0.56-3.88, 0.43) |
| ACPA positivity | 1.46 (0.70-3.06, 0.31) | 1.01 (0.39-2.64, 0.98) |
|  Lower socioeconomic status (lower level of education) | 1.93 (1.07-3.47, 0.03) | 1.97 (1.08-3.61, 0.03) |



OUTCOMES & PROGNOSIS II

DRUG-FREE REMISSION

DRUG SWITCHES

Remission is the optimal treatment target; yet, rates of remission remain low.

A significant and troubling minority of patients remain refractory to multiple DMARDs.

Can we predict sustained drug-free remission in RA?

Can we predict multiple DMARD switches in RA patients?

WHAT IS KNOWN & QUESTIONS?

GOAL: **SUSTAINED** CLINICAL REMISSION

IMAGING

Power
Doppler +
predicts flare

TISSUE

Residual
synovitis
predicts flare

SEROLOGICAL

ACPA + an
independent
predictor of
flare

DISTINCT CIRCULATING LYMPHOCYTE SUBSETS DISTINGUISH FLARE FROM DRUG-FREE REMISSION IN RHEUMATOID ARTHRITIS

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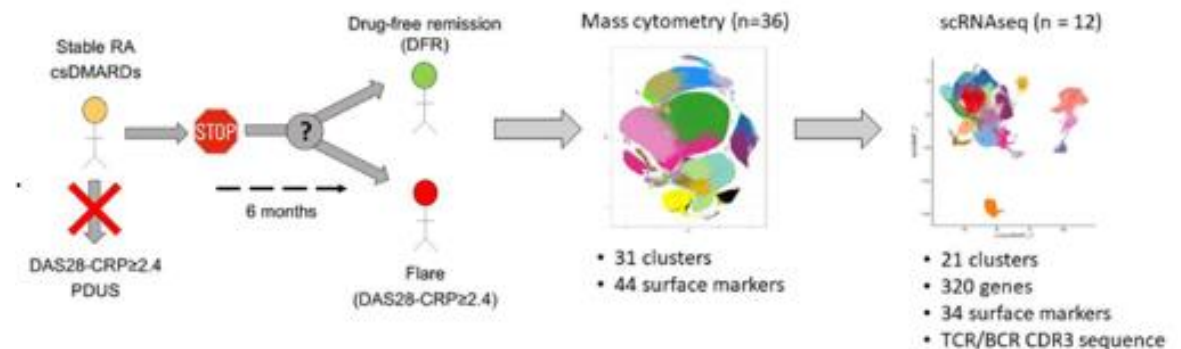
⁴Newcastle University, Genomics Core Facility, Newcastle upon Tyne, United Kingdom

❖ Study Objective

- To identify circulating lymphocyte subsets associated with RA flare and potential cellular biomarkers to predict flare versus drug-free remission (DFR).

❖ Methods

- Analysis of peripheral blood mononuclear cells (PBMCs) from patients recruited to the BioRRA study, a prospective clinical trial of csDMARD cessation.
- Patients with RA in clinical and ultrasound remission stopped csDMARDs; 6 month follow-up.



❖ Main findings

- **Significantly greater proportion of IgA+ plasma cells at flare onset versus baseline.** In contrast, a significantly lower proportion of CD25+/FoxP3+ regulatory T cells were present at csDMARD cessation (baseline) in subsequent flare versus DFR patients, suggesting biomarker potential.
- **Lower proportion of CD4+/CD25hi Tregs at baseline in flare vs drug-free remission (DFR).**

| Mass cytometry (n = 20 flare + 16 DFR) | | | |
|--|----------------------------------|--------------|-------------------|
| Contrast | Cluster | Median % | Adj. p (GLMM) |
| Flare onset vs baseline: Flare patients | CD4+/CD45RO+/PD1+ memory T cells | 2.14 vs 0.24 | <0.001 |
| | CD8+/CD45RO+/PD1+ memory T cells | 6.64 vs 0.07 | <0.001 |
| | CD19+/CD27+/CD21- memory B cells | 2.39 vs 0.03 | <0.001 |
| Single cell RNAseq (n = 8 flare + 4 DFR) | | | |
| Contrast | Cluster | Median % | Adj. p (Wilcoxon) |
| Flare onset vs baseline: Flare patients | IgA+ plasma cells | 0.37 vs 0.21 | 0.020 |
| Flare vs DFR patients: Baseline | CD4+/CD25+/Foxp3+ Treg cells | 0.55 vs 1.27 | 0.022 |

❖ Clinical relevance?

- Suggested role for CD4+ Tregs in promoting drug-free remission.
- Potential for future clinical biomarker development to predict drug-free remission & target therapy accordingly.

DIGITAL SPATIAL PROFILING REVEALS DISTINCT SYNOVIAL TISSUE MACROPHAGE TRANSCRIPTOMIC SIGNATURE OF SUSTAINED REMISSION IN RHEUMATOID ARTHRITIS PATIENTS AT RISK OF DISEASE FLARE AFTER TREATMENT CESSATION

S. Perniola^{1,2}, B. Tolusso^{1,3}, A. Elmesmari³, M. Gessi⁴, C. Di Mario¹, M. R. Gigante⁵, L. Petricca⁵, D. Bruno^{1,3}, D. Somma³, A. Paglionico², V. Varriano², L. Bui⁴, M. A. D'Agostino^{5,6}, M. Kurowska-Stolarska³, E. Gremese^{1,2,3,7}, S. Alivernini^{1,3,5,6}

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❖ Study objective

- To assess the impact of clinical classification of remission on synovial tissue (ST) features of RA in sustained remission and to identify predictive biomarkers of disease flare.

❖ Methods

- 200 RA in sustained clinical (102 RA with DAS<1.6 and 98 RA fulfilling Boolean remission criteria for at least 9 months, respectively) and ultrasound (US) remission (PD negative) on Methotrexate with or without bDMARDs were enrolled and underwent to US guided ST biopsy.
- 373 naive RA included as comparison.

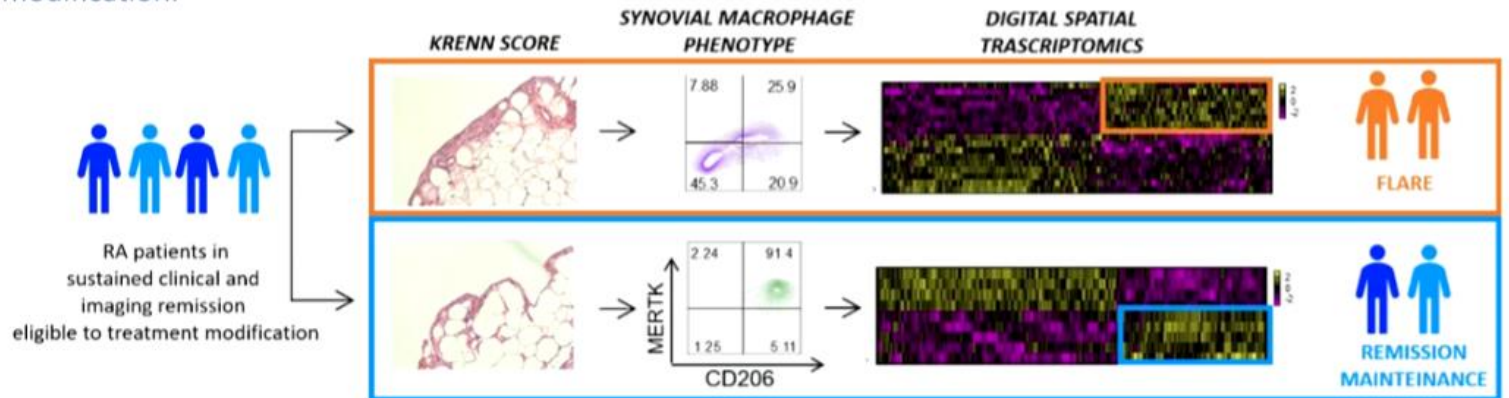
❖ Main findings

- 73(36.5%) RA patients experienced a disease flare regardless of the treatment change during 24 months follow-up.

Mild degree of residual subclinical synovitis ($KSS \geq 3$) is associated with disease flare after treatment tapering and discontinuation in RA patients in DAS- but not Boolean-defined sustained remission

Synovial tissue enrichment of MerTK^{pos} macrophages is associated with remission maintenance in RA patients in sustained clinical and ultrasound remission after treatment modification.

Digital Spatial Profiling analysis reveals unique transcriptomic signature of lining and sublining macrophages in remission RA without subclinical synovitis that is associated with subsequent disease flare after treatment modification.



❖ Clinical relevance?

- Disease flare is a common event in RA in sustained remission after treatment modification.
- High resolution technologies providing insights into cellular and molecular pathways of synovial tissue are key for delivering precision medicine in RA.
- Digital Spatial profiling has a role in providing this knowledge.

FREQUENCY AND PREDICTORS OF MULTIPLE TREATMENT SWITCHING IN RHEUMATOID ARTHRITIS

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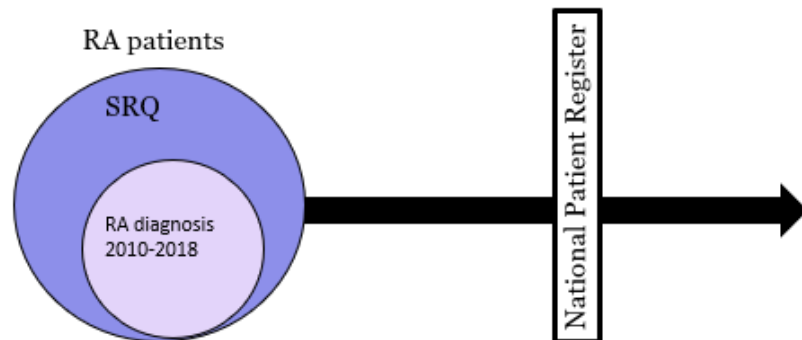
❖ Study Objective

- To assess the frequency and to identify predictors of switching between multiple biological and targeted synthetic DMARDs (b/tsDMARDs) in RA patients in a large national register.

❖ Methods

- Observational cohort study including patients with RA diagnosis between 2010-2018.
- Clinical and treatment data from the Swedish Quality Rheumatology register (SRQ).
- Comorbidities were identified through linkage to the national patient register.
- Baseline (=time of RA diagnosis) characteristics of the population regarding demographics, clinical characteristics, patient reported outcomes and comorbidities were explored.
- Three multi-switching groups were defined:
 - a) Patients starting ≥ 3 treatment courses (bDMARDs and/or tsDMARDs);
 - b) Patients starting ≥ 4 treatment courses (bDMARDs and/or tsDMARDs); and
 - c) Patients starting ≥ 5 treatment courses (bDMARDs and/or tsDMARDs).

(The timepoint for fulfilling each definition is upon the start of the 3rd (def a), 4th (def b) and 5th (def c) b/tsDMARD)
- % of patients still requiring GCs 2 years after RA diagnosis also assessed
- Predictors of multi-switching were explored using univariate and multivariable logistic regression analyses.



❖ Main findings

- 23,908 RA patients identified. Proportions of patients starting ≥ 3 , ≥ 4 or ≥ 5 b/tsDMARDs treatment courses ranged between 2-7% during the first 5 years from diagnosis.
- **Female sex, younger age, higher HAQ, pain and fatigue at baseline were independent predictors of multiple treatment switching.**
- Several **comorbidities** (heart failure, ischemic heart disease, malignancy, renal failure) were associated with a **lower risk for multiple treatment switching.**

| | All patients | Multi-switching definition | | |
|---|---------------------|----------------------------|------------------------|------------------------|
| | | A: ≥ 3 b/tsDMARDs | B: ≥ 4 b/tsDMARDs | C: ≥ 5 b/tsDMARDs |
| N, % | 23 908 (100) | 1677 (7) | 755 (3.2) | 385 (1.6) |
| Age (years), mean (SD) | 59.5 (15.2) | 50.3 (14.5) | 50.0 (14.6) | 47.6 (14.7) |
| Sex (male) % | 30.7% | 22.5% | 22.4% | 21.6% |
| CRP, mg/L (median, IQR) | 8.9 (4-22) | 10 (4-24) | 10 (4.2-25) | 10 (4-29) |
| ESR (median, IQR) | 23 (12-40) | 23 (25-39) | 23 (11-37.5) | 22 (11.8-36.3) |
| Patient global, VAS 0-100 (mean, SD) | 48.8 (26.8) | 58.4 (25.3) | 59.8 (24.5) | 60.8 (24.0) |
| Patient pain, VAS 0-100 (mean, SD) | 50.2 (26.8) | 59.2 (25.4) | 59.8 (25.2) | 59.9 (25.2) |
| Fatigue, VAS 0-100 (mean, SD) | 48.5 (28.8) | 61.2 (26.5) | 63.1 (25.9) | 64.6 (23.6) |
| HAQ (mean, SD) | 0.97 (0.66) | 1.1 3(0.64) | 1.15 (0.64) | 1.13 (0.63) |
| Swollen joint count (median, IQR) | 5 (2-9) | 6 (3-10) | 6 (3-10) | 6 (3-10) |
| Tender joint count (median, IQR) | 5 (2-9) | 6 (3-12) | 6 (3-12) | 7 (3-11.25) |
| Concomitant csDMARD, % | 52.5% | 50.4% | 51.7% | 51.4% |
| Reumatoid factor positive, % | 63.1% | 69.6% | 69.8% | 67.8% |
| ACPA positive, % | 67.0% | 73.4% | 74.3% | 72.7% |
| DAS28-ESR (mean, SD) | 4.62 (1.51) | 5.00 (1.41) | 5.10 (1.37) | 5.12 (1.33) |
| VAS general health physician (mean, SD) | 42.28 (23.02) | 45.30 (22.19) | 45.68 (20.69) | 51.40 (25.83) |

❖ Clinical relevance?

- Increased attention to the higher risk group of patients identified for drug switch could help better guide optimal management.

EULAR 2022 Highlights

Predictors, outcomes and prognosis in RA

RA is a heterogenous disease with different phenotypes at presentation; understanding these phenotypes can facilitate more optimal and targeted treatment.

Imaging investigations, namely MSKUS and MRI are valuable in predicting flares and identifying progression in pre-RA stages.

There is added clinical value in predicting radiographic outcomes when combined with clinical, serological and/or demographic markers.

Role identified for CD4+ Tregs in promoting drug-free remission.

Lower education in patients with arthralgia is associated with a higher risk of developing arthritis, partly caused by more severe subclinical joint inflammation.

Disease flare is a common event in RA in sustained remission after treatment modification.

Distinct changes in synovial tissue can predict disease flares.

Female gender, younger age, higher HAQ, pain and fatigue at the time of RA diagnosis increase risk for multiple treatment switches.

ACKNOWLEDGEMENTS

- EULAR 2022 Scientific Committee
- All mentioned speakers

THANK YOU

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