P_01

Do ethnicity, degree of family relationship, and the spondyloarthritis subtype in affected relatives influence the association between a positive family history for spondyloarthritis and HLA-B27 carriership? Results from the worldwide ASAS cohort

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Background
The Assessment of SpondyloArthritis international Society (ASAS) defines a positive family history (PFH) of spondyloarthritis (SpA) as presence of ankylosing spondylitis (AS), acute anterior uveitis (AAU), reactive arthritis (ReA), inflammatory bowel disease (IBD), and/or psoriasis in first (FDR)- or second (SDR)-degree relatives. In two European cohorts (DESIR and SPACE) a PFH of AS and AAU, but not other subtypes, were associated with human leukocyte antigen-B27 (HLA-B27) carriership in patients suspected of axial SpA (axSpA).
Objective
As the importance of ethnicity or degree of family relationship is unknown, we investigated the influence of ethnicity, FDR, or SDR on the association between a PFH and HLA-B27 carriership in axSpA suspected patients.
Methods
Baseline data from the ASAS cohort of patients suspected of axSpA were analysed. Univariable analyses were performed. Each disease (AS, AAU, psoriasis, IBD, ReA) in a PFH according to the ASAS expert definition was a determinant in separate models with HLA-B27 carriership as outcome. Analyses were stratified for self-reported ethnicity, FDR, and SDR. Analyses were repeated in multivariable models to investigate independent associations.
Results: In total, 594 patients were analysed. Patients had a mean age (SD) of 33.7 (11.7) years, 46% were male; 52% was HLA-B27+; 59% were white, 36% were Asian, 5% had another ethnicity). A PFH was reported by 23% of the patients; a PFH of AS was the most (15%) and PFH of AAU (1%) the least often reported family history among all patients. A PFH was associated with HLA-B27 carriership in patients with a white (OR:2.3, 95%CI:1.4-3.9) or Asian ethnicity (OR:3.1, 95%CI:1.6-5.8) and with a PFH in FDR (OR:2.9, 95%CI:1.8-4.5), but not with a PFH in SDR (OR:1.7, 95%CI:0.7-3.8) or in other ethnicities (Table 1). A PFH of AS was positively associated with HLA-B27 carriership in all subgroups (white OR:7.1, 95%CI:2.9-17.1; Asian OR:5.7, 95%CI:2.5-13.2; FDR OR:7.8, 95%CI:3.8-16.0; SDR OR:3.7, 95%CI:1.2-11.6). A PFH of AAU, ReA, IBD, or psoriasis was never positively associated with HLA-B27 carriership. In the multivariate analysis, similar results were found.
Conclusions
In the international ASAS cohort, a PFH of AS, but not of AAU, ReA, IBD, or psoriasis, was associated with HLA-B27 carriership irrespective of ethnicity or degree of family relationship. This cohort and two European cohorts show that a PFH of AS and possibly a PFH of AAU can be used to identify patients who are more likely to be HLA-B27 positive and therefore may have an increased risk of axSpA.

Table 1 *Univariable associations between each subtype of a positive family history and HLA-B27 carriership in chronic back pain patients suspected of axSpA included in the ASAS cohort (n=594).*

	HLA-B27+ n=310	HLA-B27- n=284	OR (95% CI)	p-value
Positive family history according to ASAS definition				
Stratified by degree of family relationship				
First-degree relatives	**79**	**31**	**2.9 (1.8-4.5)**	**<0.001**
Only second-degree relatives	15	10	1.7 (0.7-3.8)	0.212
Stratified by self-reported ethnicity				
White	**54**	**26**	**2.3 (1.4-3.9)**	**0.001**
Asian	**38**	**14**	**3.1 (1.6-5.8)**	**0.001**
Other ethnicities*	2	1	2.3 (0.2-25.0)	0.509
Positive family history of ankylosing spondylitis				
Stratified by degree of family relationship				
First-degree relatives	**61**	**9**	**7.8 (3.8-16.0)**	**<0.001**
Only second-degree relatives	**13**	**4**	**3.7 (1.2-11.6)**	**0.023**
Stratified by self-reported ethnicity				
White	**37**	**6**	**7.1 (2.9-17.1)**	**<0.001**
Asian	**35**	**7**	**5.7 (2.5-13.2)**	**<0.001**
Other ethnicities*	2	0	n.a.	n.a.
Positive family history of acute anterior uveitis				
Stratified by degree of family relationship				
First-degree relatives	5	1	4.7 (0.5-40.1)	0.162
Only second-degree relatives	1	0	n.a.	n.a.
Stratified by self-reported ethnicity				
White	4	0	n.a.	n.a.
Asian	2	1	1.9 (0.2-20.7)	0.613
Other ethnicities*	0	0	n.a.	n.a.
Positive family history of reactive arthritis				
Stratified by degree of family relationship				
First-degree relatives	3	2	1.4 (0.2-8.2)	0.735
Only second-degree relatives	0	3	n.a	n.a
Stratified by self-reported ethnicity				
White	2	2	0.9 (0.1-6.5)	0.924
Asian	1	3	0.3 (0.03-2.9)	0.302
Other ethnicities*	0	0	n.a.	n.a.
Positive family history of inflammatory bowel disease				
Stratified by degree of family relationship				
First-degree relatives	1	7	0.1 (0.02-1.0)	0.054
Only second-degree relatives	1	3	0.3 (0.03-2.9)	0.294
Stratified by self-reported ethnicity				
White	2	7	0.3 (0.05-1.2)	0.089
Asian	0	2	n.a.	n.a.
Other ethnicities*	0	1	n.a.	n.a.
Positive family history of psoriasis				
Stratified by degree of family relationship				
First-degree relatives	15	14	1.0 (0.5-2.1)	0.949
Only second-degree relatives	3	4	0.7 (0.2-3.1)	0.620
Stratified by self-reported ethnicity				
White	16	15	1.0 (0.5-2.0)	0.938
Asian	2	2	0.9 (0.1-6.5)	0.926
Other ethnicities*	0	1	n.a.	n.a.

Statistically significant results are printed in bold.* Self-reported ethnicities was missing for 5 patients, who are included in this category, and other ethnicities are black, East-Indian, Hispanic/Latino, mixed, or Turkish). ASAS, Assessment of SpondyloArthritis international Society; CI, confidence interval; HLA-B27, human leucocyte antigen B27; n.a., not applicable; OR, odds ratio.

P_02

Vascular wall inflamation in rheumatoid arthritis patients decreases after 6 months of anti-inflammatory therapy with methotrexate or adalimumab as assesed with 18f-fdg PET/CT

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Background

Patients with rheumatoid arthritis (RA) have an elevated cardiovascular (CV) disease risk, mostly explained by both an increased prevalence of traditional CV risk factors and the presence of systemic inflammation that accelerates atherosclerosis. There is accumulating evidence that anti-inflammatory treatment for RA reduces this CV risk. A non-invasive tool for detecting vascular wall inflammation in atherosclerosis is 18F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography (18F-FDG-PET/CT).

Objectives

To study the effect of anti-inflammatory treatment with methotrexate (MTX) or adalimumab on vascular wall inflammation in RA assessed by 18F-FDG-PET/CT.

Methods

18F-FDG-PET/CT was done in patients with active early RA starting MTX (n=25) and active established RA starting adalimumab (n=24) before and after 6 months of therapy, and in osteoarthritis controls (OA; n=29). 18F-FDG uptake in arterial wall was determined by standardized uptake values (SUV). Volumes of interest covering the arterial segment with the highest 18F-FDG were defined to derive the maximum SUV (SUVmax) in the ascending, descending and abdominal aorta and the aortic arch. Global arterial uptake was estimated using the mean SUVmax of the 4 arterial segments.

Results

Mean age was 65±9 for early RA, 61±7 for established RA and 63±5 years for OA controls. Median disease duration was 2.1 (interquartile range (IQR) 1.3-3.3) weeks for early RA and 6.9 (IQR 1.8-13.9) years for established RA. DAS28 was 4.9±1.0 and 4.4±1.0 at baseline and declined to 3.1±1.3 and 2.8±1.4 after 6 months therapy, respectively.

At baseline SUVmax was 1.86±0.38 for early RA, 1.68±0.43 for established RA and 1.56±0.41 for OA controls. SUVmax tended to decline more in early RA patients when compared to established RA (1.86±0.38 to 1.79±0.43 (-3.7%) and 1.68±0.43 to 1.63±0.43 (-3.0%), respectively). SUVmax in most arterial segments declined after 6 months of therapy (Table 1). The most prominent decline in SUVmax was in de abdominal aorta in established RA patients (-9.8%).

Conclusions

A decline in global arterial SUVmax and in most of arterial segments was found in both early and established RA patients after 6 months of MTX and/or adalimumab, suggesting that anti-inflammatory therapy with either MTX and/or adalimumab decreases arterial wall inflammation and thus CV risk in RA.

Table 1. Arterial 18F-FDG uptake

	OA	Early RA			Established RA		
	Baseline	*Baseline*	*6 months methotrexate*	Δ	*Baseline*	*6 months adalimumab*	Δ
SUVmax ascending aorta	1.55±0.44	1.82±0.38	1.77±0.38	-2.7%	1.69±0.61	1.60±0.44	-5.3%
SUVmax descending aorta	1.57±0.42	1.93±0.53	1.81±0.47	-6.2%	1.65±0.39	1.71±0.47	+3.6%
SUVmax abdominal aorta	1.62±0.43	1.84±0.44	1.81±0.58	-1.6%	1.73±0.61	1.56±0.45	-9.8%
SUVmax aortic arch	1.51±0.48	1.85±0.48	1.76±0.45	-4.9%	1.66±0.40	1.64±0.59	-1.2%
Mean SUVmax over 4 segments	1.56±0.42	1.86±0.38	1.79±0.43	-3.7%	1.68±0.43	1.63±0.43	-3.0%

P_03

In rheumatoid arthritis, changes in autoantibody levels do not associate with treatment response, but are a reflection of treatment intensity

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Background

Rheumatoid arthritis (RA) is characterized by the presence of autoantibodies like rheumatoid factor (RF), anti-cyclic citrullinated peptide-2 (anti-CCP2), & anti-carbamylated protein (anti-CarP) antibodies. It is currently unclear whether changes in autoantibody levels are associated with disease activity/treatment outcomes and whether they are modified by treatment intensity.

Objective

To describe the longitudinal changes in RA-autoantibody levels, the association between these changes and treatment outcomes, and the effect of treatment decisions on levels.

Methods

In 381 seropositive RA patients in the IMPROVED study[1], we measured at 4 month intervals over the first year of treatment: IgG, IgM, and IgA of anti-CCP2 and anti-CarP, IgM and IgA of RF, and autoantibodies against 4 citrullinated and 2 acetylated peptides. Following initial prednisone and methotrexate (MTX), treatment was escalated or tapered every 4 months according to whether disease activity score <1.6 had been reached. Using generalised estimating equations we investigated whether 1) baseline levels or changes in levels were associated with EULAR response at 4 and 12 months (after correction for baseline determinants), and 2) medication escalation (versus tapering) was associated with a subsequent decrease in levels.

Results

For all 14 autoantibodies, levels decreased significantly in the first 4 months and then rose until 12 months. Good EULAR response at 4 months was preceded by higher baseline levels (mean levels for anti-CCP2 IgG, a representative antibody: good-responders: 814 aU/mL; moderate-responders: 490 aU/mL; non-responders: 643 aU/mL), and good responders decreased more in levels 0-4 months than did non/moderate responders (β of 0-4 month change for anti-CCP2: good-responders: -266 aU/mL; moderate-responders: -190 aU/mL; non-responders: -194 aU/mL). However, after correction for multiple testing, this pattern was only significant for 1/14 antibodies. There was no association between EULAR response at 12 months and autoantibody levels or changes. Despite the lack of association with treatment outcomes, levels for most antibodies dropped following treatment escalation, and rose following tapering of treatment. This was best illustrated by the level decrease following the decision at 8 months to restart prednisone (on top of MTX), and rose if MTX was tapered to drug-free (Figure; significant for 12/14 antibodies after correction for multiple testing).

Conclusion

Changes in RA-associated antibody levels over time do not associate with better treatment response, but instead are a reflection of treatment intensity. This suggests that autoantibody levels are modifiable by currently available therapies, but that modifying levels is in itself of limited clinical relevance.

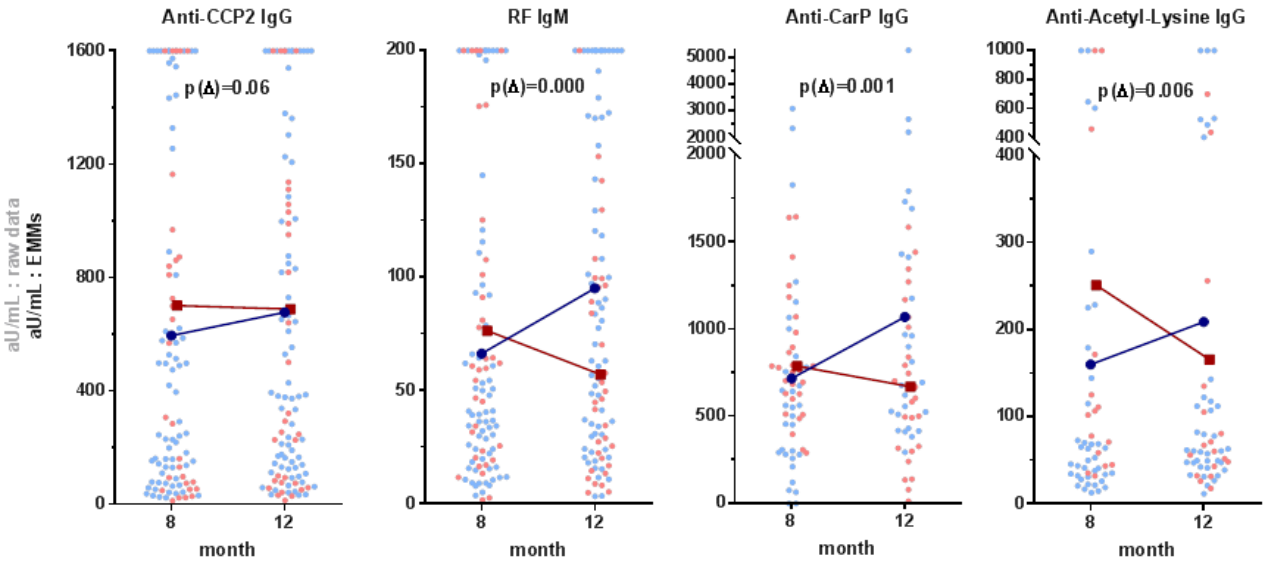

Figure: Levels in arbitrary units (aU/mL) over time for four (of fourteen) representative antibodies, separated by whether patients restarted prednisone (**red**) or tapered MTX to drug-free (**blue**) at 8 months. Dots indicate raw data; lines indicate estimated marginal means (EMMs) calculated by GEE, adjusted for age, gender, disease duration, & smoking status. *p*(Δ)-values refer to the difference in the level change over time (i.e.: slope of the lines). Anti-Acetyl. Lysine = anti-acetylated lysine vimentin.

P_04

High prevalence of clinical axial and peripheral Spondyloarthritis features in patients with Hidradenitis Suppurativa

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Background
Hidradenitis suppurativa (HS), a chronic debilitating inflammatory skin disease, and spondyloarthritis (SpA) share several pathophysiological and clinical features, such as elevated cytokine levels of TNF-α and IL-17 and the association with inflammatory bowel disease. Recognition of clinical axial and peripheral SpA features might help to identify patients with a higher chance of having SpA.

Objective
To investigate the prevalence of self-reported clinical SpA features in HS patients and to identify patient characteristics associated with these features.

Methods
In this cross-sectional study, a questionnaire concerning clinical SpA features was sent to all patients with a billing code of HS (between 2010 and 2016) in two tertiary HS referral centers in the Netherlands. First, questions were formulated based on the ASAS definitions for axial and peripheral SpA entry classification criteria: “back pain for ≥ months with age of onset <45 years” and “peripheral arthritis, enthesitis or dactylitis” in past or present, respectively. Additionally, questions concerning other clinical SpA features (Table 1) in past or present were asked. Questions were provided with proto-typical coloured pictures of SpA features for clarification. Prevalence of self-reported SpA features was calculated and comparative analysis was performed.

Results
Overall, 47.2% (620/1313) of questionnaires were eligible for analyses. Included patients had a mean age of 43±14 years, 70% were female, mean HS symptom duration was 19±13 years, mean BMI was 28±6 kg/m^2, 84% were ex- or current smokers, and 25% had no HS symptoms at the time of the survey. In total, 67.1% (416/620) of HS patients fulfilled ≥1 of the four ASAS entry criteria. The entry criteria for axial and peripheral SpA were reported by 72.8% (303/416) and 27.2% (113/416), respectively. The large majority of patients (87%) reported ≥1 clinical SpA features in addition to the entry criteria: one by 32.9%, two by 29.1%, three by 16.1%, and ≥4 by 8.9%. In comparison to patients without self-reported SpA entry criteria features (n=204), patients fulfilling the entry criteria were more frequently female ($p<0.001$), had higher BMI ($p<0.001$), more often positive smoking history ($p=0.001$), longer HS disease duration ($p=0.012$), and showed more active HS symptoms at time of the survey ($p<0.001$).

Conclusion
Self-reported clinical SpA features are common in HS patients, especially in the ‘classic’ HS patient (female, overweight, smoker), with active HS symptoms and longer HS disease duration.

P_05

Presence of IgM anti-topoisomerase I antibodies in systemic sclerosis is associated with disease progression

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Background

Anti-topoisomerase I antibodies (ATA) have been associated with severe Systemic Sclerosis (SSc), including diffuse cutaneous fibrosis (dcSSc) and interstitial lung disease. We observe however that ATA+ SSc is heterogeneous in its presentation, warranting biomarkers for additional risk-stratification to aid the clinical management of ATA+ SSc. We hypothesized that ATA characteristics such as isotype levels and positivity might be of additional help in patient stratification.

Objective

To evaluate whether clinical heterogeneity within ATA-IgG+ patients can be explained by ATA characteristics.

Methods

ATA IgG, IgM and IgA levels were assessed in consecutive serum samples of baseline ATA-IgG+ patients from the Leiden SSc cohort (CCISS). Disease progression during the first year of follow-up was defined as increase of modified Rodnan Skin Score (mRSS) with ≥ 5 points, progression of pulmonary involvement (≤ -10% of predicted forced vital capacity [FVC] or diffusion capacity of the lung [DLCO]), development of digital ulcers, renal crisis, pulmonary arterial hypertension and/or mortality. Here, we present data on the association between the presence of ATA-IgM and disease progression.

Results

In total 333 samples of 103 ATA+ patients were measured. In 29 patients there was only a baseline sample available. Median follow-up was 2.2 years (range 0.0-7.4 years). Clinical and serologic follow-up over one year was available in 67 patients. All but 1 patient were ATA-IgA+ at baseline, while only 45/74 (65%) patients were ATA-IgM+. In total, during follow-up 29 patients were considered disease progressors. Strikingly, while baseline clinical characteristics (Table 1.) did not differ between progressors and non-progressors, progressors were more often ATA-IgM+ (23/29 [79%]), compared to non-progressors (20/38 [53%]) at baseline.

Conclusion

Presence of ATA-IgM might help to identify high risk ATA+ patients and possibly explains the heterogenic disease course of ATA+ patients over time. In addition, association of ATA-IgM-positivity with disease progression indicates at an ongoing autoimmune response being relevant in disease progression.

Table 1. Baseline characteristics of ATA-IgG+ SSc patients with or without disease progression during one year follow-up

	progressor (n=29)	non-progressor (n=38)	p
Demographic and disease duration			
female, n(%)	19 (66)	29 (76)	0.33
age, mean[yrs.]±SD	55±15	51±15	0.20
since onset first non-Raynaud symptom, median [yrs.] (IQR)	3.4 (0.7-6.3)	3.0 (0.7-12.0)	0.67
Organ involvement			
dcSSc, n(%)	13 (45)	19 (50)	0.15
modified Rodnan Skin Score, median (IQR)	4 (3-9)	5 (2-14)	0.86
FVC, mean [% of predicted] ±SD	91±18	90±25	0.76
DLCO, mean [% of predicted] ±SD	65±17	61±16	0.36
myocardial involvement, n(%)	2 (7)	0 (0)	n.a.
history of renal crisis, n(%)	1 (3)	1 (3)	1.00
digital ulcers, n(%)	0 (0)	5 (13)	0.06
ATA characteristics			
IgG level[aU/mL], median(IQR)	755 (361-1127)	338 (114-946)	0.06
IgA positivity, n(%)	29 (100)	37 (97)	1.00
IgA level [aU/mL], median(IQR)	5374 (2003-15722)	2424 (585-6807)	0.04
IgM positivity, n(%)	23 (79)	20 (53)	0.04
IgM level [aU/mL], median(IQR)	933 (533-3122)	508 (223-1436)	0.06

P_06

The multi-biomarker disease activity score tracks response to rituximab treatment in rheumatoid arthritis patients

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Background

A multi-biomarker disease activity (MBDA) score was developed to objectively measure disease activity for patients with rheumatoid arthritis (RA).[1] The MBDA score is calculated by an algorithm using concentrations of 12 serum biomarkers. The MBDA score has been shown to track response to treatment with several DMARDs.[2-4]

Objectives

To assess the ability of the MBDA score to track response to rituximab treatment in RA patients.

Methods

Data were used from 3 cohorts (1 in the United Kingdom, 2 in the Netherlands) of RA patients treated with rituximab 1000 mg and methylprednisolone 100 mg at days 1 and 15. The MBDA score was assessed in serum samples at baseline (BL, n=57) and at 6 months (n=46). Wilcoxon signed-rank test was used to statistically compare the medians at BL and 6 months. Spearman's rank correlation (r) was used to analyse relationships between BL and 6 month values and change (∆) from BL to 6 months for MBDA score vs. the following endpoints: DAS28-ESR, DAS28-hsCRP, ESR, hsCRP and Health Assessment Questionnaire (HAQ). Logistic regression analysis with adjustment for age, sex, smoking, ACPA and RF was used to assess the association between ∆MBDA score and non-response, using EULAR response categories at Month 6. P <0.05 was considered statistically.

Results:At baseline the median MBDA score and DAS28-ESR were 54.5 (range 15.0-84.0) and 6.3 (range 2.5-8.4), respectively. The improvement in both scores after 6 months was statistically significant (p=0.003 and p<0.0001, respectively). MBDA score correlated with DAS28-ESR, DAS28-hsCRP, ESR and hsCRP at BL and Month 6, respectively (Table 1). ∆MBDA score from BL to Month 6 correlated with changes in these measures, except for the correlation with DDAS28-hsCRP (r=0.419, p=0.053). Spearman's correlation forDMBDA score vs. DDAS28-ESR was r=0.548, p<0.0001 (Table 1). ∆MBDA score also correlated with EULAR non-response (n=39), with adjusted OR=1.115 (95%CI=1.017-1.223, p=0.015), which corresponds to an OR of 2.97 for every 10-unit change in MBDA score. Correlations were not observed between MBDA scores or ∆MBDA score and the corresponding HAQ measurements (Table 1).

Conclusions

We have shown, for the first time, that the MBDA score tracked disease activity in RA patients treated with rituximab and that change in MBDA score reflected the degree of treatment response.

References

1 Centola M et al.Development of a Multi-Biomarker Disease Activity Test for Rheumatoid Arthritis.PLoS One.2013;8(4).
2 Bakker MF et al.Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study.Ann Rheum Dis.2012;71(10):1692–7.
3 Jurgens MS et al.The Multi-biomarker Disease Activity Test for Assessing Response to Treatment Strategies Using Methotrexate with or without Prednisone in the CAMERA Trial-II.2014;81-98.
4 Hirata S et al.A multi-biomarker disease activity score tracks clinical response consistently in patients with rheumatoid arthritis treated with different anti-tumor necrosis factor therapies: A retrospective observational study.Mod Rheumatol.2015;25(3):344–9.

Table 1. Correlations (Spearman's ρ) between the MBDA score and clinical or biomarker endpoints based on measurements made at baseline (BL) or 6 months (6M), and of change (Δ) from BL to 6 months.

Endpoint	Timepoint or period for comparison with MBDA score	Available samples (N)	Spearman's ρ	p-value
DAS28-ESR	BL 6M Δ	46 40 37	0.487 0.478 0.548	0.001 0.002 <0.0001
ESR	BL 6M Δ	44 41 41	0.765 0.670 0.448	<0.0001 <0.0001 0.006
DAS28-hsCRP*	BL 6M Δ	23 23 23	0.488 0.488 0.419	0.015 0.032 0.053
hsCRP*	BL 6M Δ	24 23 23	0.801 0.814 0.678	<0.0001 <0.0001 0.001
HAQ	BL 6M Δ	39 40 33	-0.031 -0.056 0.132	0.854 0.730 0.466

BL: MBDA score and endpoint at baseline; 6M: MBDA score and endpoint at Month 6; Δ: changes in MBDA score and endpoint, both from baseline to Month 6;
DAS28: disease activity score using 28 joints; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; hsCRP: high-sensitivity C-reactive protein; MBDA: multi-biomarker disease activity.
* United Kingdom cohort only

P_07

First results of the rheumatoid arthritis handscan registry leeuwarden

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Background

The handscan is a new technological device which uses diffuse optical transmission in combination with blood flow modulation for assessment of joint inflammation by patients with rheumatoid arthritis. It is a non-invasive measurement of the disease activity potentially more sensitive than the clinical evaluation of the joints by a rheumatologist[1]. However, more clinical data is necessary before this new device can be implemented in the daily clinical practice.

Objectives

This study investigates the additional value of the handscan in decision making in the daily practice for patients with rheumatoid arthritis.

Methods

At our outpatient clinic we started a registry for rheumatoid arthritis patients with a disease duration of at least two years. During a follow up period for two years, a handscan will be made for all patients before every regular visit. Both the patient and the treating rheumatologist will be blinded to the handscan outcome. Primary outcome is the association between DAS28 score and the total optical score (TOS) of the handscan per visit.

Results

The study started in December 2017, by the end of January 2018 100 patients were included. The mean age was 61.1 years, the mean disease duration at time of inclusion 11.2 years, 67% were rheumatoid factor positive, 51% were anti-CCP positive. In figure 1 we show the association between DAS28 and the TOS in a linear model. Currently there is no validated cut off point for the TOS (negative or positive score for inflammation). In our group of 100 patients the median TOS was 10, the most discriminating TOS was found to be 17 using chi-square test as depicted in table 1.

Conclusions

In this preliminary evaluation of the first 100 patients, we observed a limited positive correlation between the total optical score of the handscan and the DAS28. The TOS above 17 associates with moderate to severe disease activity. The definite clinical value of the handscan needs to be determined with longitudinal measurements and it's predictive value versus the DAS28. The ongoing current registry aims to answer these questions.

Figure 1: The association between DAS28 and the TOS in a linear model

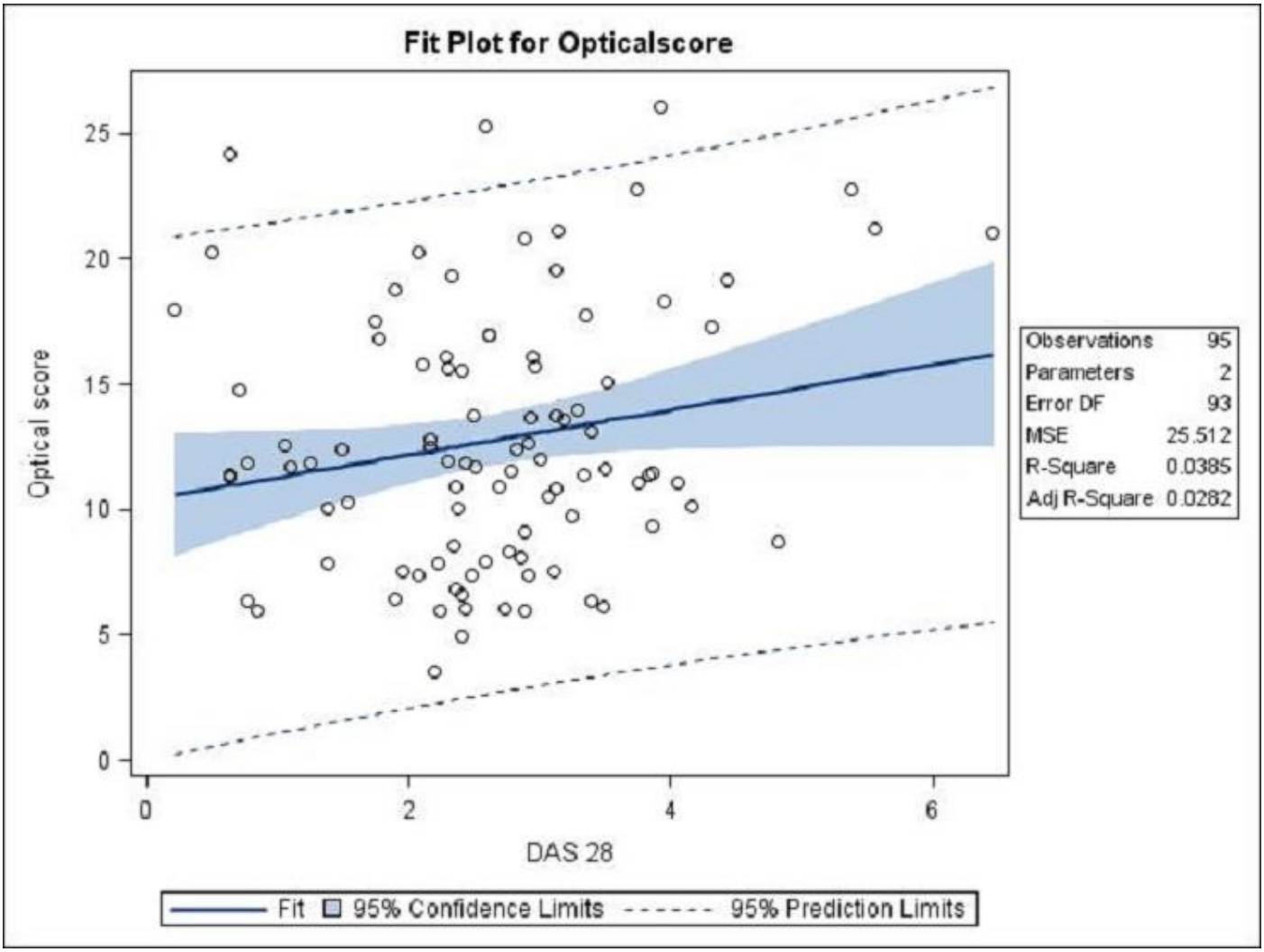

Figure 2: Shows that the TOS value of 17 is the most discrminating point of disease activity

Table 1: DAS28

		Optic score < 17	OPtic score 17 or more	Total	P-value
DAS28	Mean	2.54	3.07	2.65	0.068 (T)
	Std	0.90	1.72	1.12	
	Median	2.55	3.13	2.61	
	Q1 - Q3	2.16 - 3.12	1.89 - 4.31	2.10 - 3.25	
	Min - max	0.63 - 4.82	0.21 - 6.46	0.21 - 6.46	
	N	76	19	95	
		(4 missings)	(1 missing)	(5 missings)	

W = p-value Wilcoxon test (two-tailed)
T = p-value t test (two-tailed)
C = p-value Chi-square test
F = p-value Fisher exact test (two-tailed)

P_08

Anti-U3RNP antibodies and myocardial involvement in patients with Systemic Sclerosis

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Background
Anti-U3RNP (anti-fibrillarin) antibodies occur in 5-8% of the systemic sclerosis (SSc) population. It has been suggested that SSc patients with anti-U3RNP antibody have increased risk of myocardial involvement. As myocardial involvement is a leading cause of death in patients with SSc, it is of great importance to investigate whether anti-U3RNP positive SSc patients have a higher risk for myocardial involvement.

Objective
To evaluate the association between anti-U3RNP antibodies and myocardial involvement in patients with SSc.

Methods
All anti-U3RNP positive patients from the Leiden Combined Care in SSc (CCISS) cohort and an equal number of anti-topoisomerase antibodies (ATA) and anticentromere antibodies (ACA) positive controls matched for age and sex are included. All patients underwent extensive cardiopulmonary screening as part of the annual care program. We defined myocardial involvement according to the Medsger subdomain reflecting myocardial involvement and a combined value consisting of at least two of the following: arrhythmias, conduction problems, decreased left ventricular ejection fraction (LVEF), diastolic or systolic dysfunction on echocardiography and pericardial effusion. Baseline characteristics and cardiac parameters were compared between groups using non-parametric test, chi-square analysis and fisher exact test where appropriate.

Results
In the CCISS cohort, in total 18 anti-U3RNP positive patients (3%) were identified; these were mostly females (78%), with a mean age of 48 years. Compared to age and sex matched ACA positive and ATA positive controls, anti-U3RNP positive patients were more often African-American. Compared to ACA positive patients, anti-U3RNP positive patients had more often diffuse cutaneous involvement (p=0.024). Mean mRSS score was highest among ATA positive patients (p=0.044 U3RNP vs ATA). None of the single parameters reflecting myocardial involvement nor presence of myocardial involvement defined according to the Medsger scale or according to the combined endpoint differed between the groups. Strikingly, although presence of interstitial lung disease on imaging was lower among U3RNP patients, these patients showed the same level of impairment in VO2max as ATA patients.

Conclusion
Based on the current data we cannot confirm the association between presence of anti-U3RNP antibody in systemic sclerosis and myocardial involvement that has been suggested before. Whether the impairment in VO2 max can be explained by vasculopathy of the cardiopulmonary system needs to be determined in larger patient groups. Possibly, additional characteristics including degree of vasculopathy as shown by nailfoldcapillaroscopy can be of value.

Baseline Characteristics	U3RNP+ (n=18)	ACA + (n=18)	ATA + (n=18)
Age in years, mean (SD)	48.3 (4.0)	53.9 (3.7)	51.9 (3.8)
Female,n (%)	14 (77.8)	14(77.8)	14 (77.8)
Disease duration,median (IQR)	6.1 (8.7)	15.4 (16.8)	6.4 (13.8)
Race not caucasian, n (%)	8 (44)*	4 (22)	4 (22)
Race African American	4 (22)*	0 (0)	0 (0)
Hypertension. n (%)	6 (33.3)	3 (16.7)	3 (16.7)
Prior cardiac event, n (%)	2 (11)	2 (11)	1 (5.6)
Skin			
SSc type, n(%)	18 (100)	18 (100)	18(100)
LcSSc	9 (50)	16 (89)	8 (44)
DcSSc	7 (39)*	1 (6)	9 (50)
Other	2 (11)	1 (6)	1 (6)
mRSS, median (IQR)	5 (8)	2 (3)	8 (12) *
Digital ulcers, n (%)	2 (11)	2 (11)	4 (22)
Pitting scars, n (%)	7 (39)	6 (33)	11 (61)
Lung			
ILD on HRCT, n (%)	4 (22.2)	2 (11)	7 (39)
DLCO mean (SD)	71.4 (5.2)	77.1 (5.7)	65.8 (4.3)
DLCO < 60%, n (%)	5 (27.8)	2 (11.1)	7 (38.9)
FVCpred, mean (SD)	93.4 (6.0) *	110 (6.5)	94.3 (6.5)
FVCpred <70%, n (%)	3 (16.7)	1 (5.6)	5 (27.8)
Heart			
VO2max, mean (SD)	75.9 (7.6) *	104.2 (6)	82.7 (5.8)
VO2max < 80%, n(%)	8 (44.4)	4 (22.2)	8 (44.4)
Pericard effusion, n (%)	2 (11.1)	1 (5.6)	2 (11.1)
Arrhytmias, n (%)	2 (11.1)	3 (16.7)	5 (27.8)
Conduction problems, n (%)	5 (27.8)	3 (16.7)	5 (27.8)
Medsger score > 1, n (%)	0 (0)	1 (5.6)	2 (11.1)
Diastolic dysfunction, n (%)	1 (5.6)	1 (5.6)	1 (5.6)
Systolic dysfunction, n (%)	0 (0)	0 (0)	0 (0)
LVEF < 50%, n (%)	1 (5.6)	3 (16.7)	1 (5.6)
E/A ratio < 0.8, n(%)	2 (11.1)	6 (33.3)	3 (16.7)
E/A ratio > 2, n (%)	2 (11.1)	0 (0)	2 (11.1)
sPAP > 35mmHg, n (%)	0 (0)	1 (5.6)	1 (5.6)
TR velocity > 2.8 m/s, n(%)	3 (16.7)	2 (11.1)	3 (16.7)
Troponine > 14 ng/L, n (%)	3 (16.7)	4 (22.2)	6 (33.3)
proBNP > 247 ng/L, n(%)	3 (16.7)	2 (11.1)	7 (38.9)
CK > 145 U/L, n (%)	2 (11.1)	4 (22.2)	5 (27.8)

Table 1. *significance difference $p<0.05$. U3RNP significant more African Americans, U3RNP group significant more diffuse cutaneous SSc compared with ACA, mRSS significant higher in ATA group compared with U3RNP, FCVpred and VO2max significant lower in U3RNP and ATA group compared with ACA group.

P_09

Dynamics in peripheral blood cell counts in Giant Cell Arteritis before treatment, during treatment and in treatment-free remission

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Giant cell arteritis (GCA) is an inflammatory disease of large vessels requiring long-term treatment with glucocorticoids. The immunopathology is characterized by vessel infiltrating innate and adaptive immune cells. In GCA, only limited data on dynamics in blood cell populations before, during and after treatment are available. Moreover, it is unknown whether patients that reached treatment-free remission are truly cured or are still suffering from ongoing subclinical vasculitis. This analysis aims to document effects of short and long-term glucocorticoid treatment on leukocyte subsets in this elderly population and may provide clues on the immunopathology of GCA.

Newly-diagnosed GCA patients (not yet on treatment, n=41) were prospectively studied for a median of 914 days. Absolute numbers of leukocyte subpopulations and other standard lab parameters were measured at fixed time points. Values were compared with age-matched healthy controls (n=52). Treatment free remission was defined as absence of symptoms without immunomodulatory treatment for at least 6 months.

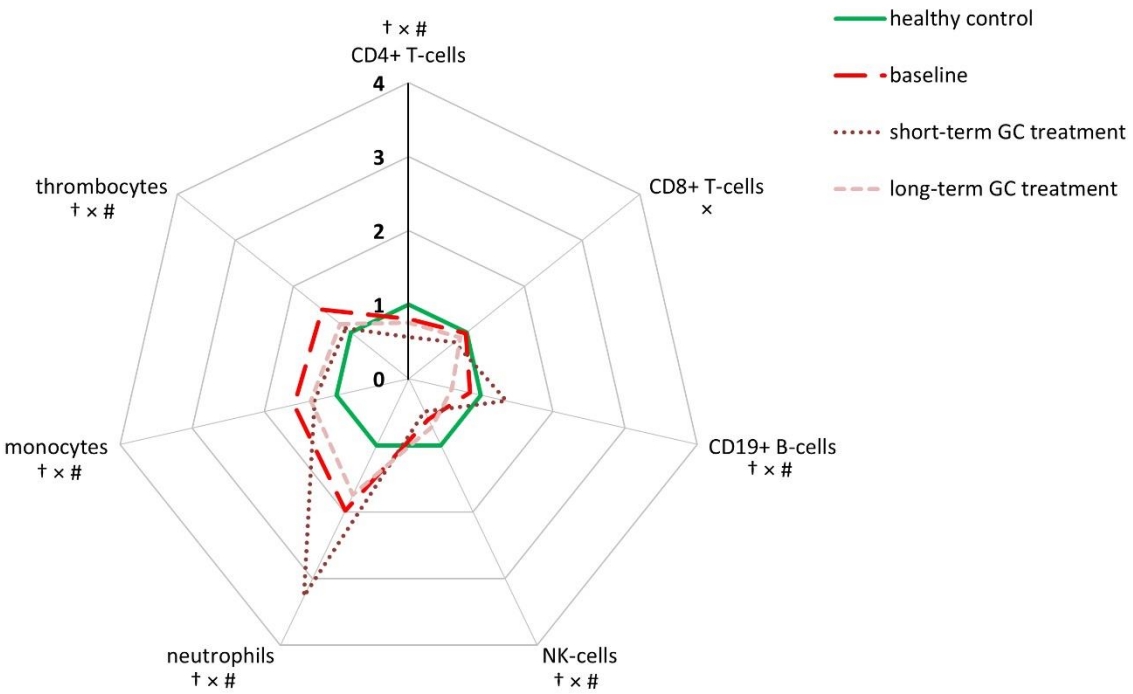
Monocyte, neutrophil and thrombocyte counts were significantly increased in newly-diagnosed GCA patients compared to healthy controls, while NK-cells were decreased. Inflammatory markers such as CRP and ESR, correlated with monocyte counts, only.

During short-term treatment (up to 3 months), most cell populations decreased but neutrophils and B-cells increased compared to baseline GCA. After 12 months of treatment, T-cells, NK-cells and neutrophils returned to baseline GCA levels, while B-cells, monocytes and thrombocytes were decreased. When compared to healthy controls monocytes, neutrophils and thrombocytes were significantly increased after 12 months of treatment while B-cells, CD4+ T-cells and NK-cells were decreased.

In samples of GCA patients in treatment-free remission, thrombocytes and innate immune cells did not normalize to healthy control levels. Monocytes, neutrophils and thrombocytes remained significantly increased, whereas NK-cells remained decreased.

In GCA, innate rather than adaptive immune cells show major fluctuations before and during treatment. These fluctuations in innate immune cells persisted even in treatment-free remission. Whether this reflects development of a new immune balance or an ongoing subclinical vasculitis remains to be investigated.

Figure 1. Changes in cell populations in GCA patients. Cell populations counts at baseline (n=41), during short-term (n=69) and long-term treatment (n=100) were expressed as a median fold-changes compared to healthy controls(n=52). † indicates significant differences between healthy controls and baseline GCA samples(Mann-Whitney U test $P<0.05$). × indicates significant differences between healthy controls and short-term treatment samples ($P<0.05$). # indicates significant differences between healthy controls and long-term treatment samples ($P<0.05$)


† × #
CD4+ T-cells
4
3
2
1
0
CD8+ T-cells
×
CD19+ B-cells
† × #
NK-cells
† × #
neutrophils
† × #
monocytes
† × #
thrombocytes
† × #
healthy control
baseline
short-term GC treatment
long-term GC treatment

P_10

The 'APPROACH' study: a 2-year, European, cohort study to describe, validate, and predict phenotypes of of knee osteoarthritis using clinical, imaging, and biochemical markers

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Background

There is a major, unmet need for more effective (bio)markers to improve the quality and effectiveness of clinical trials in the field of osteoarthritis (OA). Markers could be used to prospectively identify subjects that will show significant OA progression, help identify phenotypes of knee OA that would potentially benefit from a specific targeted therapy, and serve as outcome parameters. Having such markers would lead to investigational and therapeutic approaches which are stratified for OA phenotypes instead of the current 'one size fits all' approach as well as efficient outcome assessment.

Objective

The goal of the APPROACH study is to identify markers for knee OA, and with that, give an impulse to the development of OA treatments.

Methods

Tibiofemoral OA patients, will be selected from five European OA cohorts according to a stepwise protocol, using multiple prediction models. All prediction models have been derived using a machine-learning approach, trained on follow-up data from the Cohort Hip & Cohort Knee (CHECK) and the Osteoarthritis Initiative (OAI). The 300 patients that are most likely to experience pain and/or structural progression over 2 years according to this model will participate in the 2-year follow-up study. If needed, additional patients will be recruited from outpatient departments.

At each study visit, a set of conventional and novel markers will be obtained. Potential, novel markers will be studied using epigenetic, transcriptomic, proteomic, lipidomic and metabolomic analyses, and using novel radiographic imaging, quantitative and qualitative MRI imaging, live imaging techniques for visualizing inflammation in hands, and motion analysis techniques.

Anticipated results

Combinations of conventional and innovative markers at baseline and 6 months will predict the likelihood for OA progression at 12 and 24 months (either pain, structural, or both pain and structural), identify different OA phenotypes and valid surrogate endpoints for efficient trial design.

Conclusions

APPROACH will provide valuable insights into conventional and novel (bio)markers for OA. These markers will improve the ability to predict OA progression and distinguish between OA phenotypes. Ultimately, this will form the basis for phenotype-targeted treatments and will decrease the required number of subjects and duration for trials of potential DMOADs.

Acknowledgements

This work has received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking (APPROACH grant n° 115770).

Disclaimer

This communication reflects the views of the authors and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein.

Investigation schedule of the APPROACH cohort study

	Screening	BL	6M	12M	24M
History	X	X	X	X	X
General physical examination					
- Height	X				
- Weight	X	X	X	X	X
- Waist circumference		X	X	X	X
- Blood pressure and pulse rate		X	X	X	X
Joint examination					
- Knee	X	X	X	X	X
- Hand		X	X	X	X
- Hip		X	X	X	X
Radiography					
- Index knee	X		X	X	X
- Contralateral knee		X			X
- Hands		X			X
CT-scan					
- Index knee		X			X
- Whole Body Low Dose CT (WBLDCT)		X			X
MRI-scan of index knee					
- Quantitative MRI		X	X	X	X
- Semi-quantitative MRI		X	X	X	X
- T2 MRI		X	X		
HandScan		X			X
Motion analysis		X	X		X
Performance-based tests					
- 40m self-paced walk test		X	X		X
- 30 second chair stand-up test		X	X		X
Questionnaires					
- KOOS	X	X	X	X	X
- HOOS		X			X
- ICOAP index knee		X	X	X	X
- ICOAP hip		X			X
- FIHOA		X			X
- Pain NRS index knee	X	X	X	X	X
- Pain NRS other joints	X	X	X	X	X
- Pain DETECT		X	X	X	X
- SF-36		X	X	X	X
- One month pain diary		X	X	X	X
Biological samples					
- Blood		X	X	X	X
- Urine		X	X	X	X

BL: Baseline. **BMI:** Body Mass Index. **CT:** Computed Tomography. **MRI:** Magnetic Resonance Imaging. **KOOS:** Knee injury and Osteoarthritis Outcome Score. **HOOS:** Hip disability and Osteoarthritis Outcome Score. **ICOAP:** Intermittent and constant OA pain questionnaire. **FIHOA:** Functional Index for Hand OsteoArthritis. **NRS:** Numeric Rating Scale. **SF-36:** Short form 36

P_11

A cluster randomized controlled trial to evaluate different referral strategies for inflammatory rheumatic diseases in primary care patients: A study protocol

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Background

Considering the importance of getting the right patient at the right location to maintain and optimize the quality of life of inflammatory rheumatic disease patients, appropriate referral by general practitioners is essential. However, general practitioners have difficulties with recognizing inflammatory rheumatic diseases [1]. This study aims to assess the effect and cost effectiveness of different referral strategies for inflammatory rheumatic diseases in primary care patients by comparing them with usual care.

Methods

This study follows a cluster randomized controlled trial design where primary care clinics are regarded as clusters. General practitioners from Southwest-The Netherlands are invited to participate. They are randomly assigned to either one of the two strategic interventions for referring adult patients who are in the opinion of the general practitioner suspected of an inflammatory rheumatic disease: 1) Standardized referral algorithm based on existing referral models PEST, CaFaSpA and clinical suspect arthralgia; 2) Triage by a rheumatologist in the local primary care clinic. The control group will consist of newly referred patients to the rheumatology outpatient clinic of the Maasstad Hospital without interference of one of the referral strategies (usual care).

The effect of the referral strategies will be measured at three different levels: Patient reported outcomes (quality of life), process (number of appropriate referrals by general practitioners) and costs (work productivity and healthcare resources utilization). The primary outcome is the percentage of patients diagnosed with an inflammatory rheumatic disease by the rheumatologist after twelve months. Secondary outcomes are quality of life, work participation and healthcare costs. These data, including demographic and clinical parameters, are prospectively collected at baseline, three, six, and twelve months.

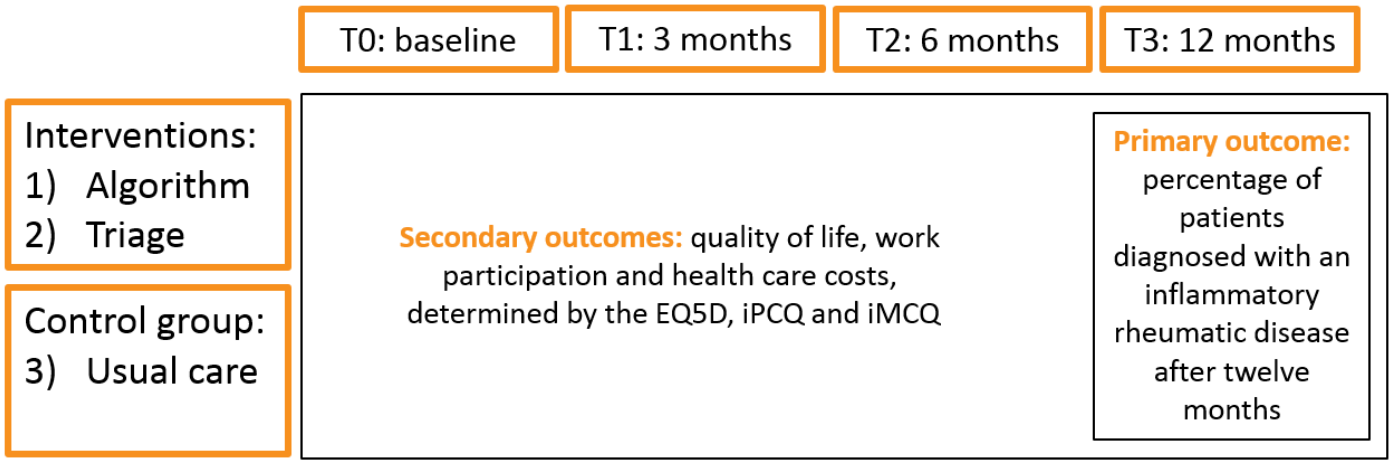
Discussion

Our target is to include ~900 patients with 296 patients in each study group (power level 0.8). It is anticipated that using the triage and/or the algorithm referral strategy for primary care patients will improve the appropriate referrals to the rheumatologist [2], and thereby improving cost-effectiveness. If this study can demonstrate improvements in health outcomes and cost-efficiency, there is sufficient supporting evidence to implement one of the referral strategies as a standard of care. Finally, with these optimization strategies a higher quality of care can be delivered, that might be of value for all patients with arthralgia.

Trial registration

NCT03454438, date of registration; March 5, 2018 (Clinicaltrials.gov)

Figure 1. Study design including study groups, timepoints and outcome measures.



P_12

Longitudinal follow up of anti-topoisomerase I positive patients within the Leiden systemic sclerosis cohort - prognosis infaust?

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Background

Systemic Sclerosis (SSc) is known for its heterogeneous disease course, ranging from mild disease with limited skin involvement (lcSSc) and >90% 5-year survival to diffuse cutaneous skin involvement (dcSSc) with decreased 5-year survival (between 50-84%). Anti-topoisomerase I antibodies (ATA) are associated with dcSSc and interstitial lung disease and therefore regarded as marker for high-risk disease according to the National Care Pathway (Zorgpad Systemische Sclerose NVR).

Objective

To describe disease course in ATA+ SSc patients.

Methods

Data of ATA+ patients included in the Leiden Systemic Sclerosis cohort (CCISS) between April 1st 2009 and May 1st 2016 were collected. Medsger Disease Severity Scale (DSS), providing a 0-4 score on 9 organ systems (0 normal to 4 severely affected; organ systems: general, peripheral vascular, skin, joint/tendon, muscle, GI tract, lung, heart and kidney) were calculated in all patients at baseline. Maximum disease score was determined, taking disease duration into account by stratifying the patients in 3 groups: 1. incident cases, 2, early disease, disease duration since first non-Raynaud =< 5 years, 3. prevalent disease, disease duration since first non-Raynaud > 5 years. Disease progression over time with specific focus on pulmonary involvement was assessed. For this purpose Kaplan Meier analysis assessing deterioration towards severe lung involvement (Lung DSS ≥3) was performed in patients with non-severe lung involvement (Lung DSS ≤2), with stratification for baseline severity score.

Results

Ninety-five patients were included in the current study. At baseline, median disease duration since first non-Raynaud symptom was 2.7 years (IQR 0.7-9.3). Forty-nine (52%) patients had lcSSc. Evaluation of disease severity at baseline showed that mild / moderately severe disease (DSS scale 0, 1 and 2) was present among all subgroups including in 36% of patients with disease duration > 5 years (Figure 1). Longitudinal follow-up was available in 85 patients, with a median follow-up time of 3.2 years. Disease progression occurred in 48 patients (57%) and 2/49 lcSSc patients developed dcSSc over time. Of the 60 patients with non-severe pulmonary involvement at baseline, 9 (15%) developed severe pulmonary involvement over time, in which baseline Medsger Disease Severity Scale was a significant predictor (Figure 2).

Conclusion

ATA+ SSc has a heterogeneous disease course, in which more than one-third of patients never develop severe organ involvement. Patients with normal lung function tests including FVC ≥70% at baseline are unlikely to develop severe lung disease during follow-up.

Figure 1. Systemic Sclerosis maximum disease severity scores according to disease duration

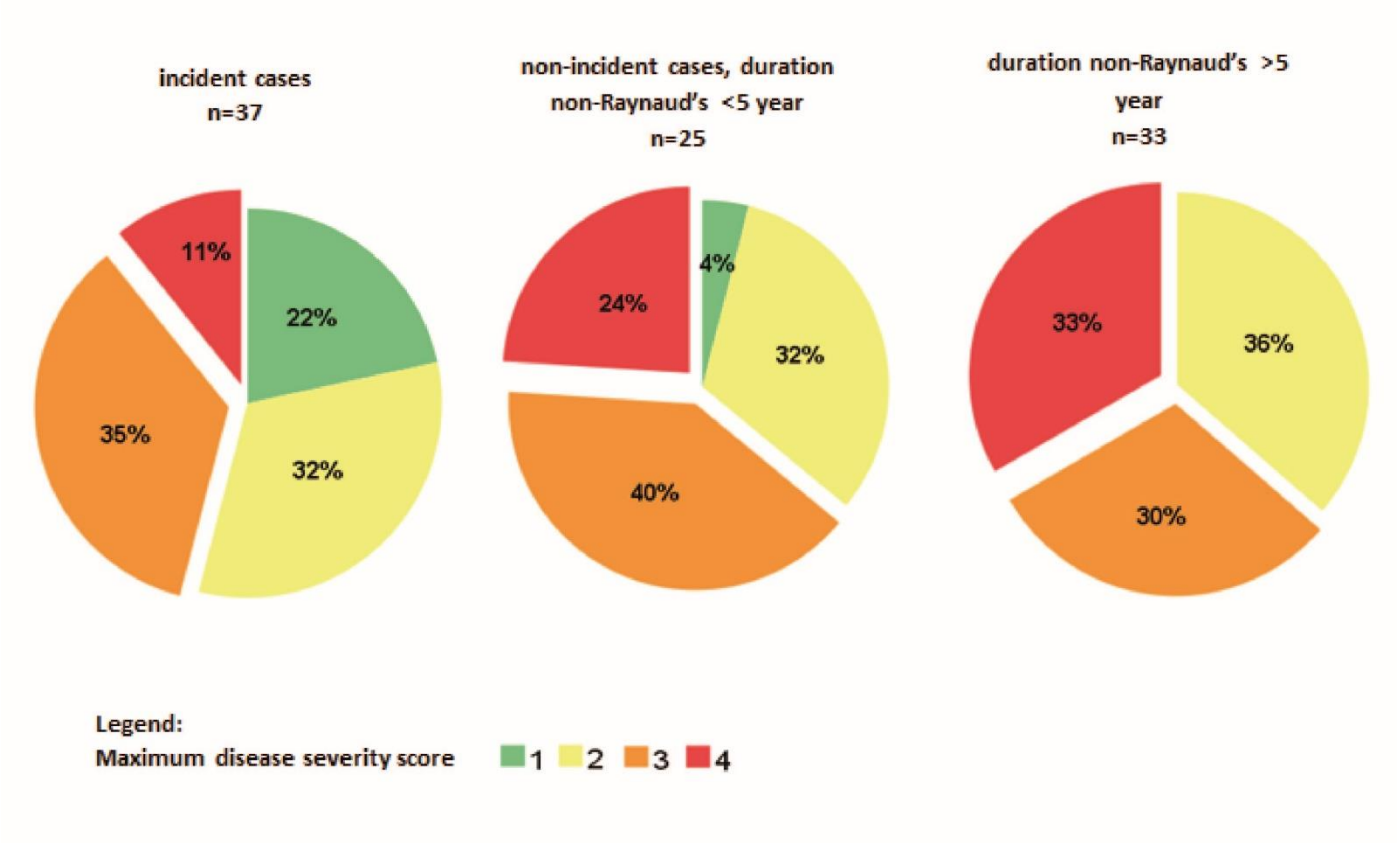
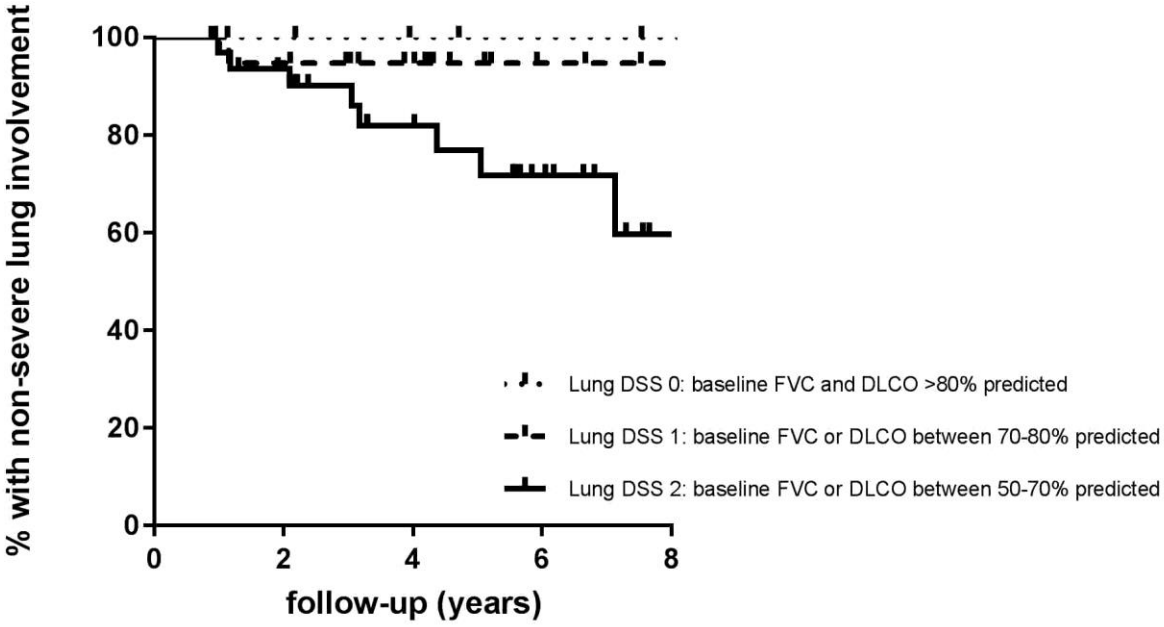


Figure 2. Kaplan Meier curves for time to development of severe lung involvement (FVC or DLCO % predicted <50%)



Number at risk

Lung DSS 0	7	5	3	3	1
Lung DSS 1	20	18	3	3	1
Lung DSS 2	33	27	18	10	2

P_13

Initial Structural Response Predicts Long-Term Survival of Knee Joint Distraction as a Treatment for Knee Osteoarthritis

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Background
In younger end-stage knee osteoarthritis (OA) patients, total knee arthroplasty (TKA) brings the risk of future revision surgery. The joint-preserving knee joint distraction (KJD) provides clinical and structural improvement for at least five years and postpones TKA. This study evaluates long-term clinical and structural results and identifies characteristics predicting native knee survival after KJD.

Methods
TKA-indicated tibiofemoral OA patients (n=20; age<60 years) were treated with KJD. WOMAC questionnaires and VAS pain scores were used for clinical evaluation at baseline and every year post-treatment, up to nine years. Minimum and mean joint space width (JSW) and mean bone density of the most affected compartment (MAC) were measured using KIDA software on standardized radiographs (baseline, one, two, five and seven years after treatment). The mean MAC cartilage thickness was measured on MRI scans (baseline, one, two, and five years after treatment). KJD survival was analyzed (failure defined by TKA) and predicted by logistic regression analyses.

Results
Three patients withdrew consent. Nine years after treatment, survival was 48%. Survival percentages differed for gender (women 14%, men 70%; p=0.035; figure 1A) and first-year minimum JSW increase (<0.5mm increase 0%, >0.5mm increase 72%; p=0.002; figure 1B).
Survivors reported clinical improvement compared to baseline: ΔWOMAC +29.9 points (SEM 5.5; p=0.001; figure 1C), ΔVAS -46.8mm (SEM 6.4; p<0.001). At seven years, a significant increase in minimum JSW (+0.62mm; SEM 0.21; p=0.020; figure 1D) but not mean JSW (+0.36mm; SEM 0.51; p=0.505) was found. In patients whose treatment failed, last-reported clinical scores were still improved: ΔWOMAC +20.5 points (SEM 9.7; p=0.067; figure 1C), ΔVAS -25.4mm (SEM 9.6; p=0.030). The last-reported minimum JSW (+0.22mm; SEM 0.16; p=0.205; figure 1D) and mean JSW (+0.21mm; SEM 0.56; p=0.712) were no longer increased.
Male gender and first-year minimum JSW increase predict nine-year native knee survival (OR 14 and 101; both p<0.046). The first-year bone density decrease and mean cartilage thickness increase had a predictive tendency (OR 0.73 and 170; both p<0.090).

Conclusions
Joint distraction for end-stage knee OA shows long-lasting clinical and structural improvement with 48% survival at nine years. Clinical scores in patients failing treatment were still improved compared to baseline and cannot (fully) explain the subsequent TKA. Native knee survival predictors are male gender and a larger initial minimum JSW increase. Potentially, an initial bone density decrease and cartilage thickness increase are predictive as well. Overall, the initial structural response after KJD seems important for long-term TKA postponement.

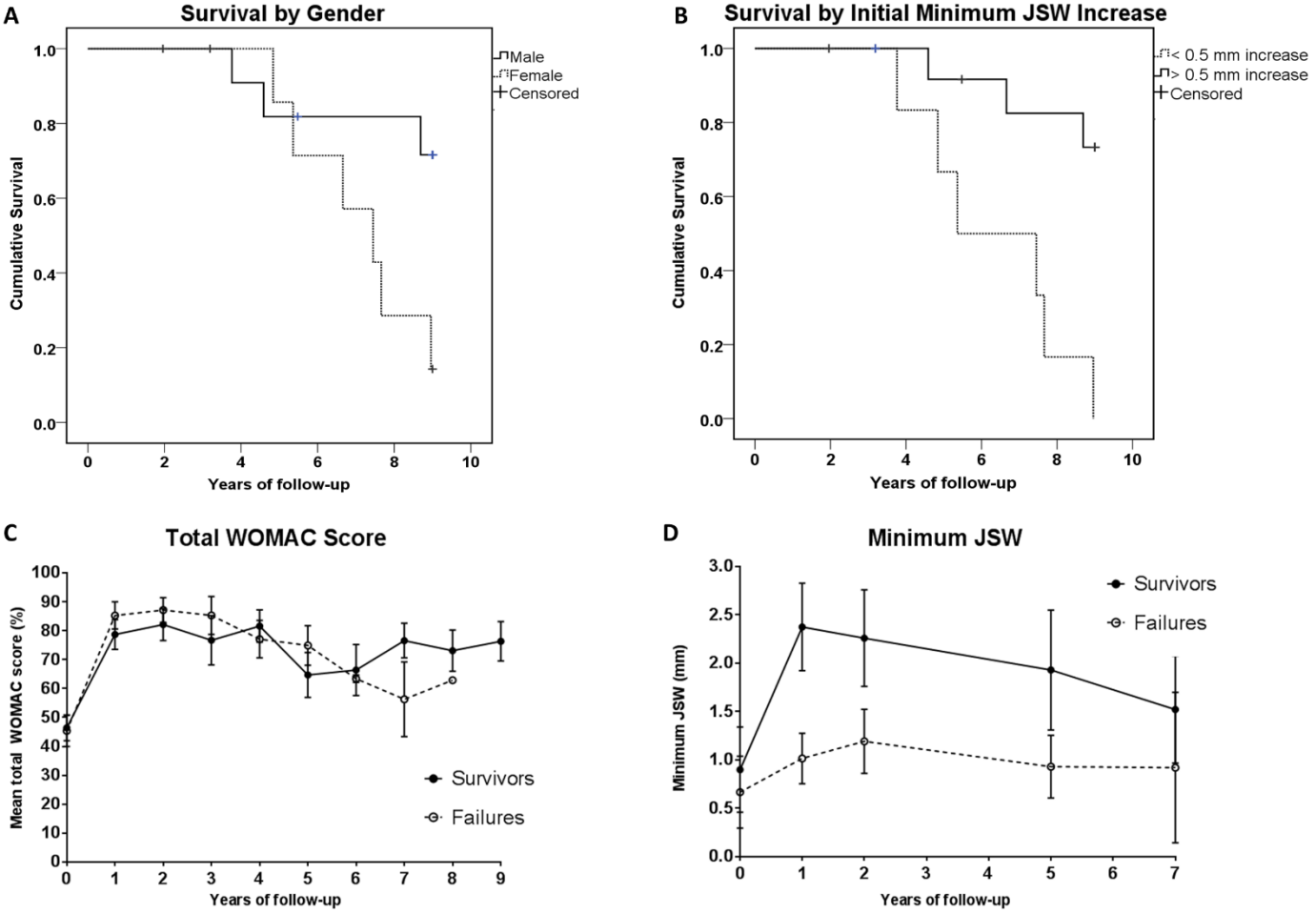

Figure 1 Long-term response after treatment with knee joint distraction. (A) Kaplan-Meier survival curves by gender, men (n=11) versus women (n=9), and (B) by increase in minimum joint space width one year after treatment, less than 0.5mm increase (n = 7) versus more than 0.5mm increase (n = 13). (C) Total WOMAC score change over nine years and (D) minimum joint space width change over seven years, separated by survivors and patients whose treatment failed within nine years. Mean values ± SEM are given.

P_14

Elucidating the role of the lymphatic system in the pathogenesis of psoriasis and psoriatic arthritis

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Background

Psoriatic arthritis (PsA) is a destructive form of arthritis that can develop in ±30% of patients with psoriasis (PsO). The IL-23–IL-17A axis is thought to be critical for both diseases, and $CD4^+$ T helper 17 cells (Th17) have been put forward as key drivers of the immunological response. The mechanisms behind the propagation of PsO into PsA are largely unknown. An impaired lymphatic system may play a crucial role, greatly affecting the migration pattern of skin-residential immune cells.

Objective

We hypothesize that lymphatic endothelial cells (LECs), core components of the lymphatic system, can control migration of pathogenic Th cells by influencing their homing properties and differentiation.

Methods

Primary human dermal LECs, and for comparison, fibroblast-like synoviocytes (FLS) of a PsA-patient were pre-incubated for 3 days with or without activation with synovial fluid of established PsA-patients. Then, allogeneic memory $CD4^+$Tcells ($CD45RO^+CD25^{-/dim}$) were added and stimulated with soluble αCD3/αCD28. After three days, T-cells and LECs were magnetically separated with anti-CD45 beads and subsequently analyzed for chemokine receptors (CCR), cytokine production, and transcription factor expression with flow cytometry and RT-qPCR.

Results

We found that healthy dermal LECs induce expression of the skin-homing receptor CCR10 and IL-22 production in memory $CD4^+$ T cells. In contrast, FLS, as well as synovial fibroblasts from a non-inflamed joint, promote Th17 cell generation by inducing CCR6 and CCR4 expression and IL-17A production. Healthy dermal LECs that were pre-incubated with synovial fluid, induce even more CCR10 expression on memory $CD4^+$ T cells. In line with the flow cytometry data, we found an increased expression of the aryl hydrocarbon receptor (AHR), as compared to the Th17 master transcription factor RAR-related orphan receptor gamma (RORC), in the cocultured memory $CD4^+$ T cells. Initial studies of the underlying mechanisms suggest that blocking the non-canonical NFB pathway downstream of the lymphotoxin beta receptor (LBTR) impairs the capacity of the LECs to suppress Th17 generation.

Conclusion

In conclusion, dermal LECs influence homing receptors on memory $CD4^+$ T cells and skew them more to Th22 cells than Th17 cells. Blocking the non-canonical NFB pathway downstream of the lymphotoxin beta receptor (LBTR) abrogated this capacity in the LECs. Future studies that compare LEC from human skin with LECs from other relevant biological tissues including synovium, lymph nodes, entheses in PsO and PsA are underway.

P_15

The importance of proper handling of human synovial fluid for arthritis research

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Background

Synovial fluid (SF) is commonly used for diagnostic and research purposes as it is believed to reflect the local inflammatory environment. Synovial fluid cells and inflammatory mediators are most often used as biomarkers of inflammation. Owing to its complex composition and especially the presence of hyaluronic acid, SF is usually viscous and non-homogeneous, hampering subsequent analyses. Although treatment with hyaluronidase can lead to homogenization of SF, this is not consequently performed in arthritis research.

Objectives

To determine the effect of hyaluronidase treatment on quantification and identification of SF cells and soluble mediators.

Methods

SF was obtained from the knee of 12 arthritis patients (9 rheumatoid arthritis, 2 osteoarthritis and 1 juvenile idiopathic arthritis patients) as part of standard clinical care. For cell analysis, synovial fluid was first centrifuged and the pellet was separated from the fluid. The fluid was subsequently treated with hyaluronidase and centrifuged again to isolate remaining cells. Cell numbers and phenotype were determined using flow cytometry. For soluble mediator measurements, 6-10 aliquots were taken and treated as represented in figure 1 resulting in set 1 and set 2. Set 1 contains replicates taken form SF before hyaluronidase treatment while set 2 mimics replicates which are taken after hyaluronidase treatment. Interleukin (IL)-8 was measured by ELISA and a total of seven fatty acid and oxidized fatty acid levels were determined using LC-MS/MS in all aliquots.

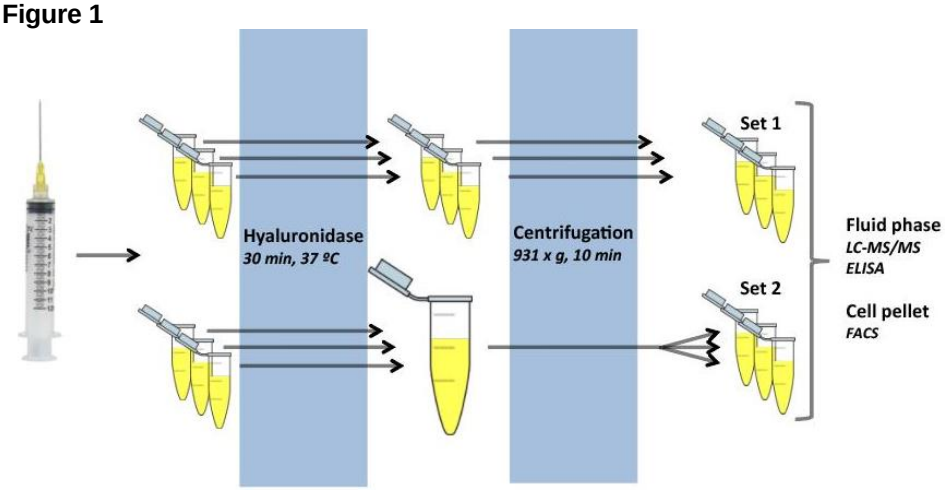
Results

Between 0.8-70% of immune cells (median 5 %) are lost when the SF is not treated with hyaluronidase. This percentage is higher for T and B cells: 7-85% (median 22%) and 7-88% (median 23 %), respectively. To assess the variation between the soluble mediator concentrations in set 1 and set 2, the coefficients of variation (CV) of the replicate measurements were compared. Aliquots in set 2 showed a lower CV for the oxidized lipids 17-HDHA, leukotriene B_4 and prostaglandin E_2 for all patients tested. For IL-8, the oxidized lipid 15-HETE, and fatty acids arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), it did not matter whether the aliquots were taken before or after hyaluronidase treatment.

Conclusions

Without hyaluronidase treatment, up to 70% of the synovial fluid cells can be lost during analyses, leading to erroneous conclusion especially when investigating rare cells populations like antigen specific B or T cells. In addition, cytokine and lipid level measurements are less accurate and largely variable between different aliquots.

Figure 1



P_16

How to treat rheumatoid arthritis patients when methotrexate has failed?

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Background

After failure of methotrexate as initial treatment in rheumatoid arthritis (RA) patients, various treatment options can be considered. To date, evidence about the preferred follow-up strategy in terms of early as well as sustained response is sparse.

Objectives

To compare consecutive DMARD-treatment regimes in daily practice in RA-patients who failed on initial methotrexate monotherapy.

Methods

Newly diagnosed RA-patients who had failed initial treatment with methotrexate were selected from METEOR, an international, observational registry. Subsequent DMARD-treatment regimens were categorized as: 1) csDMARD(s) only (143 patients), 2) csDMARD(s) + glucocorticoid (278 patients) and 3) bDMARD ± csDMARD(s) (89 patients). We selected follow-up visits until switch to yet another treatment strategy occurred or until a maximum follow-up duration of 1 year. Linear mixed model analyses were performed to analyze treatment responses per treatment group (DAS) after a maximum follow-up duration of 6 and 12 months. Differences in time-to-stop treatment between treatment groups after a maximum follow-up duration of 1 year were estimated using Cox regression. Analyses were adjusted for multiple propensity scores, to correct for confounding by indication.

Results

Median follow-up duration on studied treatment was 6.9 (IQR 4.1; 9.4) months for patients receiving csDMARD(s), 7.8 (IQR 5.0; 10.2) months for patients receiving csDMARD(s) + glucocorticoid and 9.0 (IQR 6.2; 10.9) months for patients receiving treatment including a bDMARD.

We found differences in treatment response between the three treatment groups, both after 6 months (p=0.001) and after 1 year (p=0.029). Adjusted treatment effects over time stratified for treatment groups are shown in table 1. Both after 6 months and after 1 year, patients receiving a bDMARD experienced most decrease in DAS per year, followed by patients receiving csDMARD(s) + glucocorticoid and by patients receiving treatment with csDMARD(s) alone. Results of the Cox regression showed that patients receiving treatment including a bDMARD had a lower hazard for discontinuing treatment (i.e. failing or intolerance) compared to patients receiving csDMARD(s) alone [HR (95% CI) 0.38 (0.24; 0.60)], but there were no differences between csDMARD treatment with- or without a glucocorticoid [HR (95% CI 0.89 (0.66; 1.20), figure 1].

Conclusions

In this analysis of worldwide common practice data, RA-patients who had failed initial treatment with methotrexate monotherapy had a better DAS-response and treatment survival after a subsequent switch to a bDMARD-containing treatment regimen than to a regiment with csDMARD(s), with or without glucocorticoids.

Table 1. Adjusted change in DAS over time for each medication group (n patients=509)[a]

Maximum follow-up duration	6 months		1 year	
	B	95% CI	B	95% CI
csDMARD(s)	-0.73	-1.21; -0.25	-0.39	-0.66; -0.13
csDMARD(s) + glucocorticoid	-0.96	-1.33; -0.59	-0.43	-0.62; -0.23
bDMARD (± csDMARD(s))	-2.00	-2.65; -1.36	-0.91	-1.23; -0.60

[a]Results stem from linear mixed model analyses and were adjusted for multiple propensity scores. Missing data were imputed using multivariate normal imputation (30 cycles). Due to the observational nature of the database, the actual timing of follow-up visits differed per patient. Parameter estimates represent the unit of change in DAS per year.

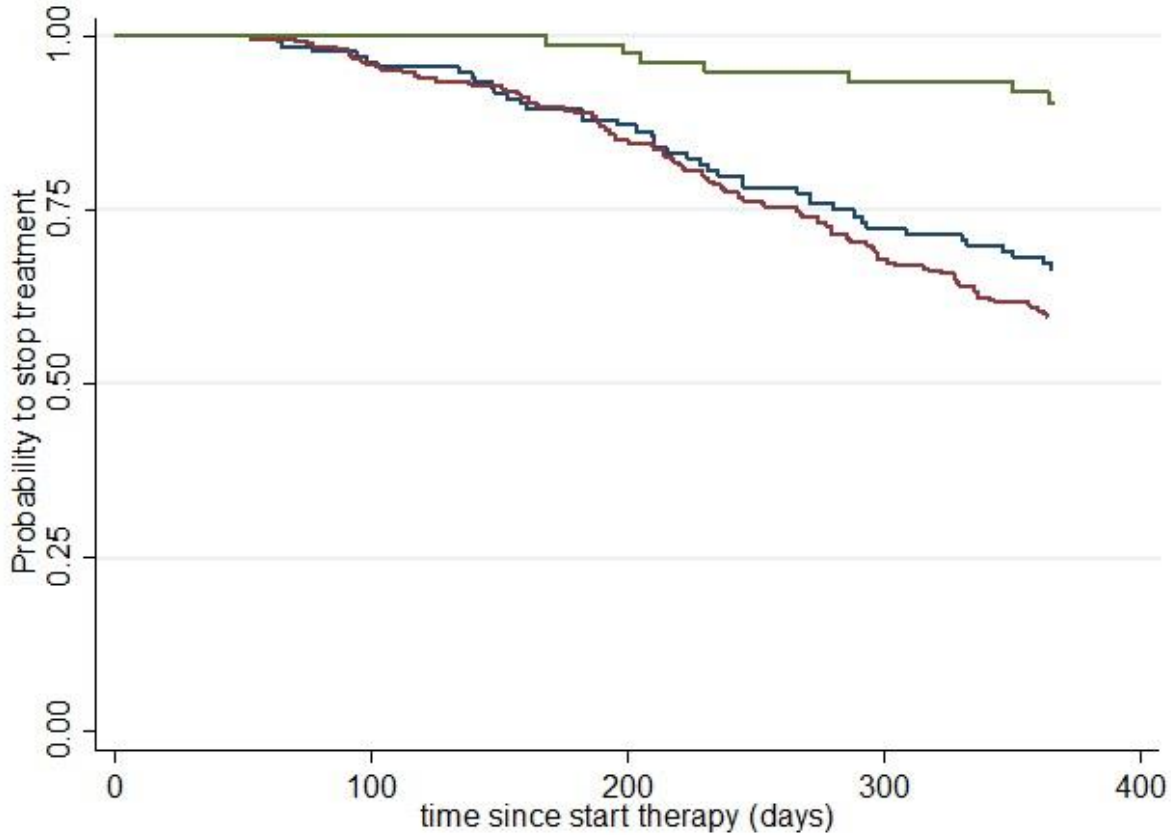

Figure 1. Kaplan-Meier curve showing the probability to stop treatment over time. The figure is based on unadjusted data. Blue line = csDMARD(s), red line = csDMARD(s) + glucocorticoid, green line = bDMARD ± csDMARD(s).

P_17

Incidence and determinants of vertebral and peripheral fractures in patients with systemic lupus erythematosus

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Background
Systemic lupus erythematosus (SLE) is associated with an increased risk of fractures[1]. However, data on the incidence of vertebral and peripheral fractures are limited. In particular, data on (morphometric) vertebral fracture incidence and determinants of such fractures are scarce and show conflicting results.

Objectives
To assess the incidence of fractures in a population of patients with SLE, and to identify determinants that predict incident vertebral and peripheral fractures.

Methods
A prospective longitudinal cohort study in 145 patients with SLE was performed. Serial bone mineral density (BMD) measurements using dual x-ray absorptiometry, and radiographs of the thoracic and lumbar spine were performed at inclusion and after a median of 5 years (IQR 3-5) follow-up. Demographic and clinical data were also collected. Vertebral fractures were scored according to the semi-quantitative method by Genant *et al.* Reported peripheral fractures were confirmed by x-rays. Analyses were performed with logistic regression (forward selection procedure, p-value of 0.05 as cut-off level). The outcome measures were incident fracture in general (yes/no), vertebral fracture (yes/no), and peripheral fracture (yes/no).

Results
Of the 145 included patients, 131 (90%) were females and 100 (69%) Caucasian. The mean age was 41 years (SD 12) at baseline, and median follow-up was 7.2 years (IQR 6-12). A total of 42 incident fractures (vertebral and peripheral) occurred during 998 patient years. The incidence rate of vertebral and peripheral fractures was 2.0 per 100 patient years (95% CI 1.30-3.13), and 2.20 per 100 patient years (95% CI 1.45-3.35), respectively.
Any fracture (both vertebral and peripheral) was predicted by postmenopausal status and Caucasian ethnicity. Vertebral fractures were predicted by age, in which the older the SLE patient, the higher the odds of getting vertebral fractures. Peripheral fractures were predicted by history of stroke, postmenopausal status and moderate alcohol use (1 – 12 units per week). Use of higher dosages of alcohol (> 13 units per week) did not reduce peripheral fracture occurrence. Table 1 shows the final prediction models.

Conclusion
The results of our study suggest a twofold increased risk of both vertebral and peripheral fractures in SLE patients compared to the general population[1,2]. Age, Caucasian ethnicity and postmenopausal status are important risk factors for incident fractures in SLE. In addition, special attention should be paid to SLE patients with a history of stroke since this subgroup of patients is at high risk of peripheral fractures.

Table 1 Multivariate logistic regression analyses of independent explanatory variables that predict incident fracture, showing OR and 95% CI

	Any fracture			Vertebral fractures			Peripheral fractures		
Variables	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Age				1.0	1.0– 1.1	0.017			
Caucasian ethnicity	13.3	1.7 – 104.3	0.014						
Postmenopausal status	4.0	1.6 – 10.1	0.004				3.2	0.86 – 11.6	0.084
Past stroke							15.5	1.1 – 212.2	0.040
Alcohol use									
- No							Ref		
- Moderate							0.06	0.01 – 0.62	0.019
- Heavy							1.9	0.14 – 24.9	0.634

P_18

Development and validation of a sensitive LC-MS/MS-based method for analysis of enzymatic activity of folylpolyglutamate synthetase and methotrexate polyglutamates in peripheral blood mononuclear cells of rheumatoid arthritis patients

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Background

Methotrexate (MTX) is a widely applied anti-rheumatic and anti-leukemic drug. For its intracellular retention and pharmacologic activity, MTX relies on the enzymatic activity of folylpolyglutamate synthetase (FPGS) to convert MTX into its polyglutamate forms (MTX-PG_{2-6}). Loss of FPGS activity is associated with reduced MTX activity and although red blood cell (RBC) MTX-PG_n levels correlate with disease activity in RA patients [1], it is anticipated to be more relevant to measure MTX-PG_n in peripheral blood mononuclear cells (PBMCs). Thus, the aim of our study was to develop a LC-MS/MS method to 1) measure FPGS activity replacing laborious radioactive assays, and 2) to measure MTX-PG_n in PBMCs [2].

Objectives

To validate a rapid, sensitive and non-radioactive assay to measure FPGS activity and MTX-PG_n in PBMCs based on LC-MS/MS technology.

Methods

Protein extracts (n=5) of PBMCs of MTX-treated RA patients were incubated for 2 hours at 37°C in FPGS assay buffer (pH8.8) containing 250µM MTX and 4mM L-glutamic acid as substrates. Next, MTX-PG_2 formation was analyzed with AB Sciex 4000 Q Trap tandem mass spectrometer coupled to an Acquity Ultra Performance LC system. Measurement of PBMC-MTX-PG_n (n=5) was performed by extraction of MTX-PG_n from PBMCs by perchloric acid precipitation. Quantification was performed with $^{13}C_5{}^{15}N$-labeled MTX-PG_{1-5} internal standards. In FPGS activity and MTX-PG validation studies, human CCRF-CEM leukemia cells, CEM/R30dm (a FPGS-deficient, MTX-resistant subline of CCRF-CEM), and human acute lymphoblastic leukemic (ALL) cells served as reference.

Results

In CCRF-CEM, the FPGS enzymatic assay showed linearity with protein input (10-250µg) and incubation time (0.5-3 hours). Substrate affinity parameters (Km) for MTX (65µM) and L-glutamic acid (2.2mM) were consistent with earlier reports [3]. FPGS activity in CEM/R30dm was <1% of CCRF-CEM. FPGS activity in ALL blasts was similar to CCRF-CEM while FPGS activity in RA patient PBMCs was 1-5% of CCRF-CEM, and was non-detectable in RBCs. Average individual fractions of total MTX-PG_n in RA patient PBMCs were 22,1% (range: 8.2-36.2%) for MTX-PG_2, 32.8% (27.1-43.6%) for MTX-PG_3, 34.4% (30.4-41.3%) for MTX-PG_4 and 10.6% (0.0-28.4%) for MTX-PG_5. Average total MTX-PG_n levels per number of RA patient PBMCs were 30-50 fold higher than matched numbers of erythrocytes, and 6-9 fold lower than ALL blasts incubated for 24 hours with 1µM MTX.

Conclusions

A sensitive LC-MS/MS based method was developed for the measurement of FPGS activity and MTX-PG_n levels in PBMCs of RA patients. This method holds promise to guide future MTX-therapy response evaluations.

P_19

Lumbale wervelkolom en heup botmineraaldichtheid stabilisatie bij patiënten met actieve reumatoïde artritis tijdens rituximab therapie

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Achtergrond

Een welbekende comorbiditeit van reumatoïde artritis (RA) is gegeneraliseerd botverlies, zich uitend in een verminderde botmineraaldichtheid (BMD).[1-2] Hoewel rituximab een frequent voorgeschreven biologisch ziektemodificerend anti-reumatisch geneesmiddel (bDMARD) is voor de behandeling van RA, zijn gegevens over veranderingen in BMD in RA patiënten tijdens rituximab behandeling beperkt.

Doel

Bepalen van de mate van BMD verandering van de lumbale wervelkolom en heup bij patiënten met actieve reumatoïde artritis behandeld met rituximab.

Methode

Opeenvolgende RA patiënten met een hoge ziekte-activiteit (DAS28> 3.2) die met rituximab behandeling begonnen, werden geïncludeerd in een prospectieve cohortstudie. BMD van de lumbale wervelkolom en heup werd gemeten vóór de behandeling en na één jaar door middel van dual energy X-ray absorptiometry (DXA). Klinische respons werd gedefinieerd met behulp van de EULAR response criteria voor RA.[3]

Resultaten

In totaal werden 43 patiënten (18,6% man) met een gemiddelde leeftijd van 53,6 (SD 10,7) jaar geïncludeerd in de studie. Bij aanvang van de studie was de mediane ziekteduur 9,5 (IQR 0,7-40,2) jaar en de gemiddelde DAS28 was 5,6 (SD 1,3). In responders trad er een significante DAS28 daling op van 1,97 punten (SD 0,78); in non-responders nam de DAS28 af met 0,01 punten (SD 0,67). Er was geen verschil in gemiddelde cumulatieve prednisondosering (5,4 mg/week in responders t.o.v. 5.0 mg/week in non-responders), bisfosfonaat (25,9% in responders t.o.v. 12,5% in non-responders) en vitamine D/calcium (44,4% in responders t.o.v. 31,3% non-responders) gebruik tussen beide groepen. Er bleek geen relatie te bestaan tussen BMD verandering en cumulatieve prednisondosering dan wel bisfosfonaat gebruik. Alle BMD veranderingen waren niet statistisch significant (tabel 1).

Conclusie

Bij patienten met actieve RA die behandeld werden met rituximab lijkt het botverlies van zowel de lumbale wervelkolom als de heup tot halt gebracht te worden, ook bij patienten zonder klinische respons. Verder onderzoek bij een grotere patiëntenpopulatie en met langere follow-upduur is noodzakelijk om de resultaten van deze studie te bevestigen.

Referenties:

1. McInnes IB et al. N Engl J Med 2011;365:2205-2219.
2. Firestein GS et al. Nature 2003;423:356-361.
3. van Gestel et al. Arthritis Rheum 1996;39:34-40.

Tabel 1 BMD-verandering na één jaar gecategoriseerd volgens de EULAR response criteria

	Gemiddelde (SD) BMD bij inclusie	Gemiddelde (SD) BMD na 1 jaar	Gemiddelde BMD verandering	% BMD verandering
LWK totaal (n=43)	1.015 (0.182)	1.011 (0.186)	-0.004	-0.4
LWK responders (n=27)	1.026 (0.169)	1.017 (0.182)	-0.009	-1.0
LWK non-responders (n=16)	0.997 (0.206)	1.001 (0.198)	0.004	+0.7
Heup totaal (n=43)	0,845 (0.144)	0,849 (0.143)	0.003	+0.5
Heup responders (n=27)	0.836 (0.126)	0.838 (0.129)	0.003	+0.3
Heup non-responders (n=16)	0.862 (0.174)	0.867 (0.166)	0.005	+0.8

BMD is weergegeven in g/cm^2; BMD; botmineraaldichtheid; LWK, lumbale wervelkolom.

P_20

Six months after treatment discontinuation TNF is still in complex with adalimumab

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Background

Many patients with rheumatoid arthritis (RA) are successfully treated with tumour necrosis factor inhibitors (TNFi). Once in remission, some patients can discontinue the TNFi for a prolonged period. Insights in TNF dynamics during and after treatment discontinuation are lacking. We recently developed a novel assay that can quantify TNF in the presence of large amounts of TNFi, i.e. a 'drug-tolerant' assay, and showed that TNF levels increased and stabilized during adalimumab due to complex forming between TNF and adalimumab. Moreover, in the presence of adalimumab, all TNF was in complex and biologically inactive.

Objective

To investigate complexed TNF levels 6 months after the last adalimumab administration.

Methods

TNF and adalimumab levels were measured using a novel drug-tolerant competition enzyme-linked immunosorbent assay (ELISA), and a regular ELISA, respectively, in 11 consecutive RA patients with stable low disease activity (disease activity score of 28 joints < 3.2) who discontinued adalimumab for 6 months (prior dose: 40 mg every 2 weeks). Blood samples were drawn prior to adalimumab discontinuation and 3 and 6 months thereafter.

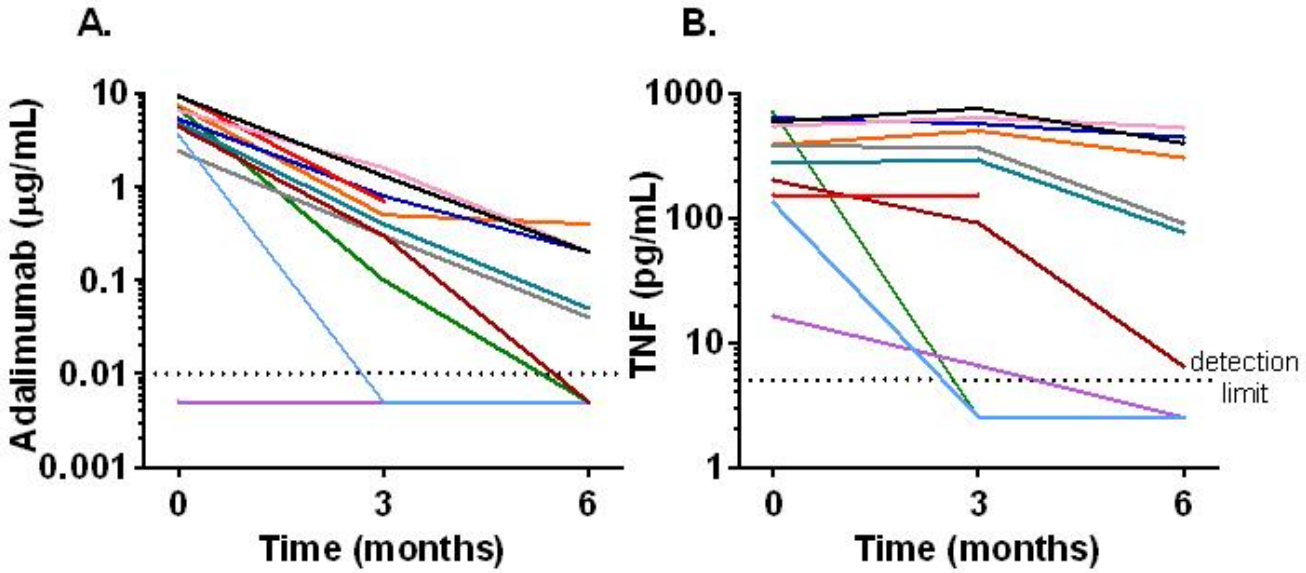
Results

Six months without adalimumab resulted in a decreased mean adalimumab concentration from 5.5 (SD 2.9) to 0.55 (0.52) and 0.11 (0.13) µg/mL at 3 and 6 months after treatment discontinuation (Figure 1A). In contrast, complexed TNF levels remained stable for prolonged periods of time: in 8 patients TNF levels at 3 months were indistinguishable from levels seen at baseline, upon on standard-dose adalimumab (Figure 1B). After 6 months, in patients with adalimumab concentrations above 0.1 µg/mL (n=4) TNF still remained stable. Overall, mean TNF levels decreased from median 381 (inner quartiles 16; 707) to 290 (2; 755) and 83 (2; 532) pg/mL at 3 and 6 months after treatment discontinuation, respectively. In 5 patients TNF levels decreased significantly. In those patients, adalimumab levels dropped to, or below the detection limit.

Conclusion

This is the first study showing that TNF is still in complex with adalimumab in the majority of patients 6 months after the last administration. Therefore, one may wonder at which point in time a patient has truly discontinued adalimumab treatment.

Figure 1: (A) adalimumab levels and (B) tumour necrosis factor (TNF) levels of 11 patients prior to adalimumab discontinuation and 3 and 6 months thereafter.



P_21

(Onvervulde) zwangerschapswens en preferentie van patiënten met betrekking tot zwangerschapscounseling bij SLE

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Achtergrond

Bij patiënten met SLE is goede counseling voor de zwangerschap en begeleiding voor, tijdens en na de zwangerschap essentieel om het risico op zwangerschapscomplicaties te minimaliseren. In VUmc bestaat sinds 16 jaar intensieve samenwerking tussen reumatologen en gynaecologen op het gebied van zwangerschapscounseling bij SLE. Het is onbekend of de huidige wijze van zwangerschapscounseling voldoet aan de behoeften van de patiënten.

Doel van de studie

Inventariseren van de wensen van patiënten met SLE met betrekking tot zwangerschap en zwangerschapscounseling.

Methode

Enquête onder 176 vrouwelijke patiënten met SLE, die deelnemen aan het longitudinale Amsterdamse SLE cohortonderzoek met behulp van een vragenlijst met 32 items. Enquête periode: 4 weken.

Resultaten

Interimanalyse van resultaten van 100/176 (57%) patiënten, van wie 60% (60/100) een of meerdere kinderen heeft gekregen, hetgeen bij 58% (28/48) was nadat de diagnose SLE werd gesteld. Van de kinderloze patiënten, was bij 23% (9/39) sprake van bewuste kinderloosheid; bij 33% (3/9) was dit op medisch advies. Ongewenste infertiliteit ten gevolge van medicatiegebruik is bij 1 patiënte opgetreden (3%;1/39). In totaal zagen 7/60 (11%) patiënten met kinderen af van een volgende zwangerschap door het beloop van een eerdere zwangerschap (complicaties/actieve SLE).
Een grote meerderheid van 84% (83/99) gaf aan kinderwens te hebben (gehad). Een eerste gesprek hierover vond bij 57% (36/63) plaats met de reumatoloog, meestal (86%;30/35) geïnitieerd door de patiënte zelf. Het tijdstip van informatievoorziening was volgens 82% (37/45) van de patiënten goed.
Patiënten geven de voorkeur aan mondelinge eerste informatievoorziening door reumatoloog (57%;36/63) of gynaecoloog (16%;10/63) boven voorlichting door paramedici.
Tevens hebben patiënten ook behoefte aan een schriftelijke samenvatting van de gegeven voorlichting (75%;45/60), informatie via folders/brochures (42%;21/50) en/of een website (34%;17/50). De meerderheid van de patiënten (56%;35/62) heeft voorkeur voor de huidige manier van voorlichten door reumatoloog en/of gynaecoloog afzonderlijk, terwijl 35% (22/62) een gezamenlijk spreekuur zou prefereren.

Conclusies

De (interim)resultaten tonen een onvervulde zwangerschapswens bij SLE patiënten. 40 patiënten zijn kinderloos, van wie 23% (9/39) bewust. Van de 60 patiënten met kinderen gaf 11% (7/60) aan af te zien van een volgende zwangerschap door het beloop van een eerdere zwangerschap.
Er is een grote behoefte aan zwangerschapscounseling, waarbij de meeste patiënten de huidige informatievoorziening door reumatoloog en/of gynaecoloog afzonderlijk en een schriftelijke samenvatting van verstrekte informatie prefereren. Een gezamenlijk spreekuur door reumatoloog en gynaecoloog kan tegemoet komen aan de wens van een minderheid van de patiënten, die voorkeur voor deze manier van zwangerschapscounseling heeft.

P_22

An indirect comparison of effectiveness and safety of three treat-to-target treatment strategies: Tocilizumab with or without MTX and MTX with prednisone

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Background

Treatment with methotrexate (MTX), often with concomitant glucocorticoids, is still the cornerstone of early rheumatoid arthritis (RA) therapy, although it might be less efficacious compared to (expensive) biological disease modifying anti-rheumatic drugs, such as tocilizumab (TCZ). Hitherto, the efficacy and safety of MTX in combination with glucocorticoids have never been compared with those of TCZ with or without MTX.

Objectives

To determine if initiation of TCZ, or of TCZ with MTX (TCZ+MTX) is more effective and safe than initiation of MTX with 10mg prednisone (MTX+Pred) in step-up treat-to-target treatment strategies in early RA patients.

Methods

Individual patient data of the U-Act-Early (*n=317*) and CAMERA-II (*n=236*) trials were indirectly compared; the MTX *(n=108+119)* strategy functioned as reference. Both were 2-year, double-blind, randomised, placebo-controlled studies evaluating step-up tight-control, treat-to-target treatment strategies[1,2]. TCZ+MTX (*n=106*) and TCZ (*n=103*) were compared with MTX+Pred (*n=117*): the primary outcome was the disease activity score (DAS28) over time. Secondary outcomes were remission, defined as DAS28<2.6, and the ConRew score (cumulative occurrence of remission and sustainment of remission). Multiple imputation was used for missing data: baseline HAQ, rheumatoid factor (RF) status and smoking status. Multi-level models were made to account for clustering of patients within trials and for repeated measurements within patients over time. All models were corrected for baseline DAS28, HAQ, RF-status and smoking using fixed (and random) effects.

Results

Significant differences at baseline were observed between CAMERA-II and U-Act-Early for RF seropositivity and DAS28; respectively 60% vs. 73%; p<0.01 and 5.7 vs. 5.2; p=0.01. DAS28 was significantly lower over time for TCZ+MTX compared to MTX+Pred (mean difference: -0.62 [95%CI -1.14 to -0.10]), but not for TCZ, Table 1. Achievement of remission occurred significantly more often in TCZ+MTX and TCZ compared to MTX+Pred: odds ratios 1.11 [95%CI 1.02 to 1.22] and 1.09 [1.00 to 1.20], respectively. ConRew scores were numerically higher for TCZ+MTX and TCZ compared to MTX+Pred, without statistically differences, Table 1. Safety outcomes were similar between the treatment strategy groups, Table 2.

Conclusion

A 2-year treat-to-target, tight controlled treatment strategy with TCZ yielded lower disease activity over time compared to a MTX+Pred strategy with similar safety profiles. These results may support the use of TCZ in early RA.

References

1. bakker MF, Jacobs JW, Welsing PM, et al. *Ann intern Med*. 2012;156;329-339.
2. Bijlsma JWJ, Welsing PMJ, Woodworth TG, et al. *Lancet.* 2016;338;343-55.

Table 1 Differences in efficacy between treatment strategies of interest based on adjusted analyses

	TCZ+MTX vs. MTX+Pred		TCZ vs. MTX+Pred	
Efficacy	**Mean difference (95% CI)**	**P-value**	**Mean difference (95% CI)**	**P-Value**
DAS28	-0.62 (-1.14 to -0.10)	0.02	-0.44 (-1.00 to 0.12)	0.08
ConRew	3.92 (-1.12 to 8.97)	0.14	4.73 (-0.41 to 9.86)	0.08
	Odds Ratio (95% CI)		**Odds Ratio (95% CI)**	
Remission	1.11 (1.02 to 1.22)	0.01	1.09 (1.00 to 1.20)	0.05

Table 2 Differences in safety between treatment strategies of interest based on adjusted analyses

	TCZ+MTX vs. MTX+Pred		TCZ vs. MTX+Pred	
Safety aspects	**Relative Risk (95% CI)**	**P-value**	**Relative Risk (95% CI)**	**P-value**
Elevated ALT	1.62 (0.66 to 3.97)	0.30	0.92 (0.33 to 2.53)	0.86
Elevated AST	1.48 (0.35 to 6.17)	0.60	0.55 (0.11 to 2.86)	0.48
Infections	0.99 (0.11 to 9.03)	1.00	1.05 (0.11 to 9.58)	0.96
Drop out due to AE	1.18 (0.39 to 3.63)	0.76	1.30 (0.43 to 3.90)	0.65

P_23

Halvering van febuxostat 80 mg filmomhulde tabletten; het urinezuur verlagende effect van (halve) 40 mg versus (hele) 80 mg tabletten in de praktijk

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Inleiding

In Netherlands en Europa is het urinezuur verlagende medicijn febuxostat voor de behandeling van jicht op de markt als filmomhulde tabletten in sterktes van 80 en 120 milligram (mg), maar niet 40 mg. In de dagelijkse praktijk kan een dosering van 40 mg soms wenselijk zijn, bijvoorbeeld om veiligheidsredenen bij patiënten met een verminderde nierfunctie. Halvering van een 80 mg filmomhulde tablet is een mogelijke oplossing, maar dit is off-label. Ook kan halvering de coatingfunctie beïnvloeden met mogelijk gevolgen voor de effectiviteit en de kans op bijwerkingen.

Doel

Onderzoek naar het urinezuur verlagende effect en de veiligheid van febuxostat in een startdosering van 40 mg per dag (als gehalveerde 80 mg filmomhulde tablet) bij jichtpatiënten in vergelijking met patiënten die 80 mg per dag gebruiken.

Methoden

Retrospectieve studie van alle jichtpatiënten binnen een ziekenhuis beginnend met febuxostat 80 mg of 40 mg (80 mg filmomhulde tabletten gehalveerd). Verzamelde gegevens: Patiënt en ziekte kenmerken, startdosis/startdatum van febuxostat, dosisveranderingen, follow-up duur, bijwerkingen, stopdatum en reden, serum urinezuur (sU) en kreatinine (sKreat) over tijd, relevante comorbiditeit. Statistisch getoetst werden baseline kenmerken (Chi-square of onafhankelijke t-test, waar van toepassing), gemiddelde sU bij baseline en na 12 weken (gepaarde t-test binnen groepen en onafhankelijke t-test tussen groepen), percentuele verandering ten opzichte van de uitgangswaarde en het percentage patiënten on target (sU lager dan 0,36 of 0,30 mmol/l) tussen groepen (onafhankelijke t-test).

Resultaten

Tussen april 2012 en juli 2017 zijn 36 patiënten gestart met febuxostat. Dertien patiënten met 40 mg en drieëntwintig met 80 mg eenmaal daags. Tabel 1 toont patiëntkenmerken en uitkomsten op gekozen parameters. sU-waarden waren beschikbaar voor 35 patiënten bij baseline en 33 patiënten hadden een eerste sU-waarde binnen 12 weken na start. Mediane follow-up was 1.6 jaar (range 0-6.7). Figuur 1 toont sU waarden over tijd.

Vijf patiënten (14%) stopten tijdens follow-up, allemaal binnen 8 weken na start vanwege bijwerkingen: diarree (n=2, 40 mg en 80 mg), coronair syndroom (n=1, 80 mg), erectiestoornissen (n=1, 40 mg) en jichtaanvallen (n=1, 40 mg). Andere mogelijke bijwerkingen waren droge mond (n=1, 80 mg), leverenzymstijging (n=1, 40 mg) en flushing (n=1, 40 mg).

Conclusies

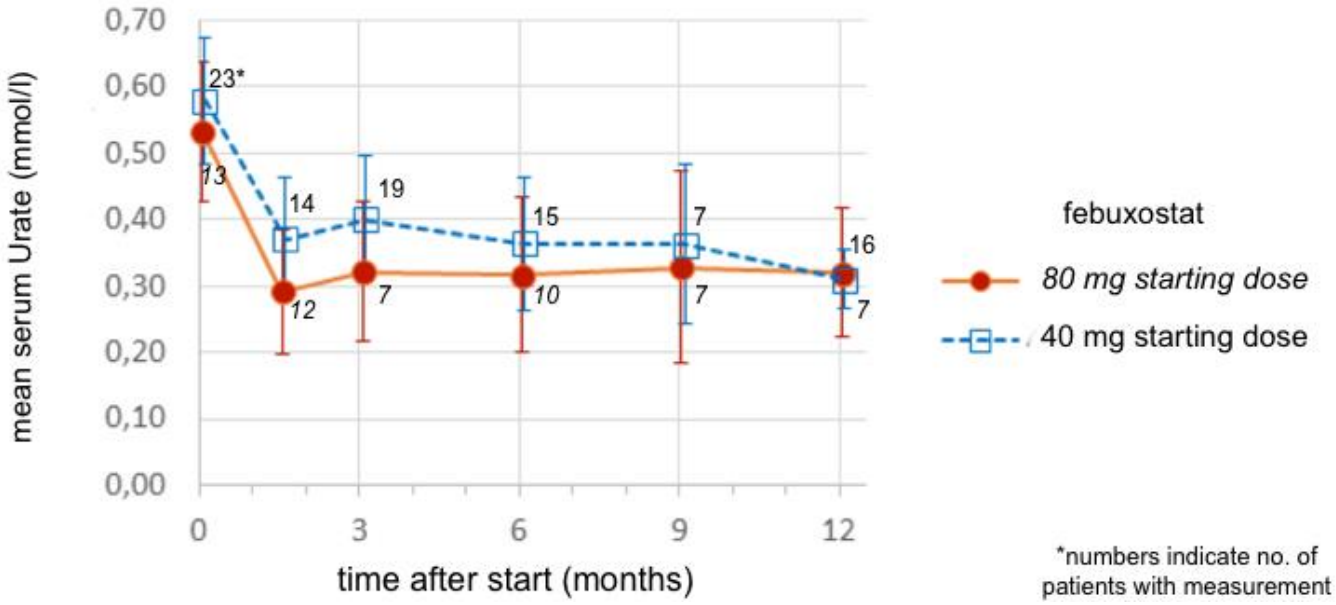
Zowel dagelijkse doseringen als febuxostat van 80 en 40 mg (80 mg filmomhulde tabletten worden in de helft gesplitst) resulteren in significante daling van sU-waarden binnen 12 weken. Een startdosis van 80 mg is mogelijk effectiever in het verminderen van het sU, vooral tot onder het 0,30 mmol/l target.

Tabel 1: baseline karakteristieken en effecten op serum urinezuur per groep

Baseline karakteristieken	Totale groep, N=36	80 mg start dosis, n=23	40 mg start dosis, n=13	p-value
leeftijd, j, mediaan (bereik)	60 (33-90)	60 (34-90)	64 (33-87)	0.68
mannelijk geslacht, n(%)	29 (81%)	21 (91%)	8 (62%)	<0.05
diagnoseduur, j, median (bereik)	1.7 (-0.1-13.0)	0.8 (-0.1-12.3)	2.9 (0.9-13.0)	0.36
kristal bewijs , n(%)	22 (61%)	15 (65%)	7 (54%)	0.79
tophi*, n(%)	15 (44%)	8 (23%)	7 (54%)	0.21
chronische nierinsufficiëntie (GFR 30-59 ml/min/1.72m2), n(%)[$]	16 (44%)	7 (30%)	9 (69%)	<0.05
andere relevante comorbiditeiten[#], n(%)	30 (81%)	19 (83%)	11 (85%)	0.88
Uitkomsten				
sU bij start, gem (SD)	0.55 (0.11)	0.53 (0.10)	0.59 (0.10)	0.25
sU na 12 weken[&], gem (SD)	0.35 (0.12)**	0.31 (0.10)**	0.39 (0.10)**	<0.01
% on target (<0.36 mmol/l)	68%	76%	57%	0.65
% on target (<0.30 mmol/l)	36%	50%	8%	<0.01
% verandering in sU, gem (SD)	35 (18)	40 (18)	32 (17)	0.67

*tophi informatie afwezig bij 2. [$]laagste GFR bij start was 30 ml/min/1.72m2. [#]diabetes mellitus, obesitas, hypertensie, hyperlipidemie, hartvaatziekten. [&]beschikbaar bij resp. 33, 21 en 12 patiënten. **P-waarden binnen groepen <0.001 t.o.v. baseline.

Figuur 2: serum uraat over tijd



P_24

The association between serum drug level of TNF-a inhibitors and disease activity in patients with axial spondyloarthritis

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Background

In approximately 50% of patients with axial spondyloarthritis (SpA) treated with TNF-α inhibitors, treatment loses efficacy after a period of time.[1] Previous research has shown that high disease activity is associated with low serum drug levels.[2] There is limited literature regarding this subject in axial SpA patients on long-term TNF-α inhibitors.

Objective

To investigate the association between trough serum drug level of TNF-α inhibitors and disease activity in axial SpA patients.

Methods

From June 2015 to June 2016 all 112 patients of the Groningen Leeuwarden Axial SpA (GLAS) cohort, fulfilling the ASAS classification criteria, treated with TNF-α inhibitors, who had a GLAS-visit at the UMCG were approached to have a trough serum drug level measurement. This needed to be performed within two months from the GLAS visit. Based on reference values of Sanquin[3], serum levels were stratified in therapeutic and below the therapeutic range. Disease activity was assessed with the ASDAS and BASDAI.

Results

67 (60%) of the 112 patients were eligible for analyses. Thirty-one (46%) were male, which was 47% of all male patients who had a consultation that year.

Mean age was 45±12 years, 48 patients (72%) were HLA-B27 positive, mean symptom duration was 20±12 years and mean duration of TNF-α inhibitor treatment was 49 months (2-141). 34 patients were on adalimumab (51%), followed by 21 on etanercept (31%). The remaining 12 patients (18%) were on infliximab, certolizumab or golimumab. Of the 67 patients with trough serum drug levels, 32 (48%) were therapeutic and 35 (52%) below therapeutic, with no significant difference in patient characteristics between these groups, including ASDAS and BASDAI, except for mean adalimumab and etanercept level (table 1).

No significant correlations for ASDAS and BASDAI with adalimumab or etanercept drug level were found (adalimumab r=-0.164, p=0.36; r=-0.191, p=0.29; etanercept r=-0.185, p=0.42; r=-0.113, p=0.63 resp.).

However, when stratified by gender, only women on adalimumab showed a significant negative correlation between serum level and ASDAS and BASDAI (r=-0.444, p<0.05; r=-0.497, p<0.05 resp.). Patient characteristics for men with and without serum trough level did not differ significantly.

Conclusion: Approximately half of the axial SpA patients on long term TNF-α inhibitor treatment had a mean serum trough level below the therapeutic range and overall no significant correlation between serum drug level of TNF-α inhibitors and disease activity was found except for women on adalimumab. Unfortunately unintended sex selection bias may have influenced our results.

Table 1: Patient characteristics stratified for therapeutic and below therapeutic TNF-α inhibitor trough level

Demographics	*Therapeutic (n=32)*	*Below-therapeutic (n=35)*
Age (mean, SD)	44 ± 13	45 ± 12
BMI (mean, SD)	27.2 ± 6.1	28.4 ± 5.0
Gender (male) (n, %)	14 (45)	18 (50)
Disease status		
Symptom duration (years)	21 ± 13	20 ± 11
HLA-B27-positive, n (%)	21 (70)	27 (82)
ASDAS	2.2 ± 1.0	2.3 ± 0.8
BASDAI	3.9 ± 2.4	4.1 ± 2.1
ASQoL	6 (0-18)	6 (0-18)
BASFI	3.1 (0.4-9.7)	3.1 (0.1-8.1)
ESR	13 (1-42)	9 (1-53)
CRP	4.5 (0.7-75)	3 (0.4-32)
Patient GDA	3 (0-9)	3 (0-10)
Physician GDA	1 (0-3)	1 (0-4)
Therapy		
Duration since start TNF-therapy (months)	50 (3-141)	49 (2-133)
Serum adalimumab level	8.0 ± 2.3	3.2 ± 1.4*
Serum etanercept level	2.6 ± 0.5	1.1 ± 0.6*

Values are mean ± SD or median (range) unless otherwise indicated. HLA B27: human leukocyte antigen B27; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASQoL: Ankylosing Spondylitis Quality of Life; BASFI: Bath Ankylosing Spondylitis Functional Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GDA: Global Disease Activity.

*Statistical difference ($p<0.001$), versus patients with a therapeutic level.

P_25

Clinical features of Sternocostoclavicular Hyperostosis: a large Single Center Dutch Cohort

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Sternocostoclavicular hyperostosis (SCCH) is a rare inflammatory bone disorder due to a chronic sterile osteomyelitis of unknown origin, leading to hyperostosis and sclerosis of sternum, medial end of clavicles and first ribs. Other areas of the axial skeleton such as mandible and vertebrae may also be affected. We report the clinical characteristics of a large single centre Dutch cohort of 189 patients with an established diagnosis of SCCH on the basis of characteristic clinical, scintigraphic and radiological features.
Data on gender, age at first symptoms and at diagnosis, clinical manifestations, shoulder girdle function, and disease-related incapacity for work, were retrieved from medical records.
The cohort consisted of 189 patients, predominantly female (88%), with a median age of 37 years (range 17-70) at first symptom. Most common first symptoms were pain in 159 patients (85%), local inflammatory changes in 77 (41%), impairment of shoulder girdle function in 63(34%), and bone swelling in the SCC region in 54 (29%). At time of diagnosis, which occurred after a mean delay of 5±5 years, main clinical manifestations were chronic pain of variable severity in the SCC region in 183(95%), bony swelling of affected areas of the anterior chest wall in 124(66%) and restricted shoulder girdle function in 81 patients(43%). 64 patients (35%) had palmoplantar pustulosis, and 47 (25%) had an autoimmune disease, mainly psoriasis (n=15, 8%). The most commonly affected sites were the medial end of the clavicles in 76% of patients, followed by medial end of first ribs in 64%. Mandible and vertebrae were less commonly affected.
SCCH is a rare inflammatory bone disorder associated with variable degrees of disability leading to potential disease-related incapacity to work due to chronic pain and impairment in shoulder girdle function. Initial symptoms may be elusive, and delayed diagnosis is common because of inability to identify the clinical features of the disorder. This may result in irreversible structural changes in the SCC region and potentially debilitating chronic symptoms. Early diagnosis and early institution of therapy may positively influence prognosis by preventing disease progression, although this remains to be established by long-term follow-up studies.

P_26

Can novel auto antibody profiling predict disease manifestations in an inception cohort of systemic sclerosis patients?

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Introduction

Auto antibodies play a prominent role in both classification and disease prognosis of systemic sclerosis. In several cohorts the association between auto antibodies and prognostic factors has been described. In recent years, new methods of antibody profiling have become available, and have shown an important prognostic role for anti-RNA polymerase III (anti-RNAP3). However, it is uncertain whether other auto antibodies have associations with complications as well.

Objective

To determine the prevalence of auto antibodies in a cohort of systemic sclerosis and to evaluate the associations with complications.

Methods

A total of 319 consecutive patients from the Nijmegen Systemic Sclerosis Inception Cohort were included. All patients fulfilled the ACR/EULAR 2013 classification criteria for systemic sclerosis. Patients were subclassified as limited cutaneous systemic sclerosis(LcSSc), diffuse cutaneous systemic sclerosis (DcSSc) or overlap syndrome according to Leroy and Medsger. Blood samples were collected and analyzed using LIA (SSc and ENA immunoblot, Euroimmun, Lubeck, Germany). Clinical data was collected prospectively.

Results

Our cohort comprises mainly Caucasians. The percentage of male and diffuse patients is higher compared to other cohorts (1) (Table 1). There is a relative anticentromere antibody (ACA) dominance in our cohort and ACA antibodies are more common in patients with pulmonary arterial hypertension (PAH), which is consistent with previous studies. Interestingly, in our cohort we found a relatively high prevalence of anti-Ro52 antibodies in patients with serious complications (Figure 1).

Conclusions

The distribution of the main auto antibodies is comparable to other Caucasian cohorts (1). Because the prevalence of anti-RNAP3 is low, it is of limited value in our population. The prevalence of anti-Ro52 was high in patients with the three major disease complications, but this auto antibody was also present in a number of patients who did not (yet) have these complications. Previous studies have shown ambiguous results concerning the relevance of this auto antibody (2). RNP/SM and RNP-70 may be associated with cardiac involvement as shown in Figure 1. To evaluate the prognostic value of anti-Ro52, RNP/SM and RNP-70 in systemic sclerosis, a large prospective cohort study is necessary.

References

1. Domsic RT et al. Scleroderma: the role of serum autoantibodies in defining specific clinical phenotypes and organ system involvement. Curr Opin Rheumatol. 2014;26(6):646-52.

2.Wodkowski M et al. Monospecific anti-Ro52/TRIM21 antibodies in a tri-nation cohort of 1574 systemic sclerosis subjects: evidence of an association with interstitial lung disease and worse survival. Clinical and experimental rheumatology. 2015;33(4 Suppl 91):S131-5.

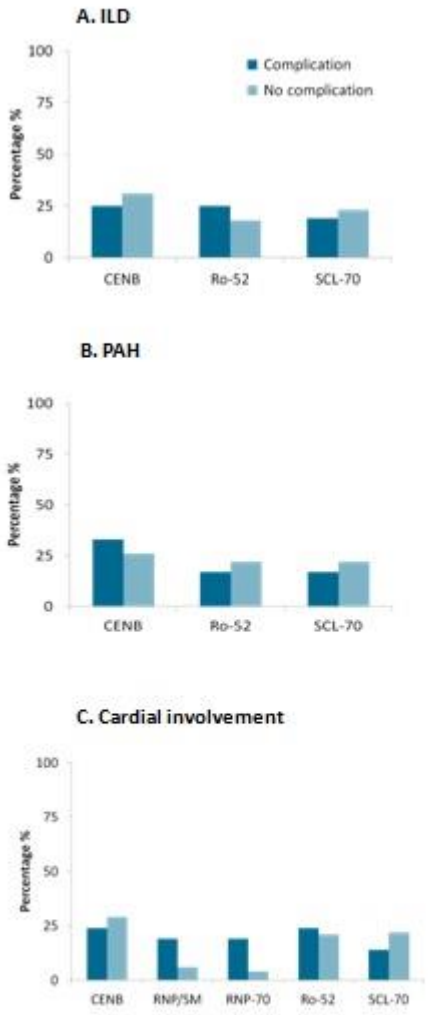

Figure 1. Prevalence of auto antibodies in SSc with and without complications. Antibodies <10% prevalent not shown. ILD interstitial lung disease; PAH pulmonary arterial hypertension.

Clinical / laboratory feature	No.	%
Total	319	
Male gender	100	31%
LcSSc	182	57%
DcSSc	102	32%
Overlap	35	11%
PAH	36	11%
ILD	134	42%
Cardial involvement	21	7%
Renal crisis	3	0.9%
ACA	90	28%
ATA	63	21%
Anti-RNAP3	14	4.4%
Anti-SSA/Ro-52	30	9.4%
RP-11	22	6.9%
RNP/SM	22	6.9%
RP-155	21	6.5%
M2-3E	21	6.5%
M2	21	6.5%

Table 1. Demographic and clininal characteristics

P_27

The link between angiogenesis and osteogenesis in spondyloarthritis

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Background

Spondyloarthritis is characterized by inflammation, extensive angiogenesis and pathological osteogenesis. Transmembrane (tm)TNF transgenic (tg) mice (1) that overexpress tmTNF exhibit features of spondyloarthritis, including chronic inflammation and pathological osteogenesis. tmTNF ligation to TNF receptor 2 in endothelial cells (ECs) can induce signal transduction pathways, that may promote these processes. Of note, angiogenesis and osteogenesis are coupled by EC differentiation towards a type H ($CD31^{hi}endomucin^{hi}$) phenotype (2). We investigated the link between pathological angiogenesis, inflammation and osteogenesis in tmTNF tg mice.

Methods

Vertebrae from 6 and 12 weeks and 8 months old tmTNF tg mice or non-tg littermates (n=18) were prepared by cutting 60 µm thick cryosections for confocal imaging.

Results

tmTNF tg mice exhibited ectopic osteogenesis which was not observed in non-tg littermates. The provided image demonstrates an ectopic lesion at the white arrow. Immunostainings showed that type H vessels are in the vicinity of the ectopic osteogenesis and $osterix^+$ osteoprogenitors. Furthermore, there is increased osteogenesis, type H vessel presence and a different vessel architecture within the vertebrae of tmTNF tg mice compared to non-tg littermates that progresses with age. Non-tg littermate vertebrae only have physiological osteogenesis, which is in the metaphysis and periosteum. In addition, tmTNF tg mice exhibit altered bone marrow (BM) architecture containing extensive lymphoid aggregates, which predominantly consisted of $B220^+$ aggregates and contain high endothelial venules.

Conclusions

tmTNF overexpression in mice leads to development of type H vessels associated with ectopic osteogenesis. In addition, extensive lymphoid aggregates develop in the BM. Current studies are aimed at identification of signaling pathways in ECs that contribute to these processes.

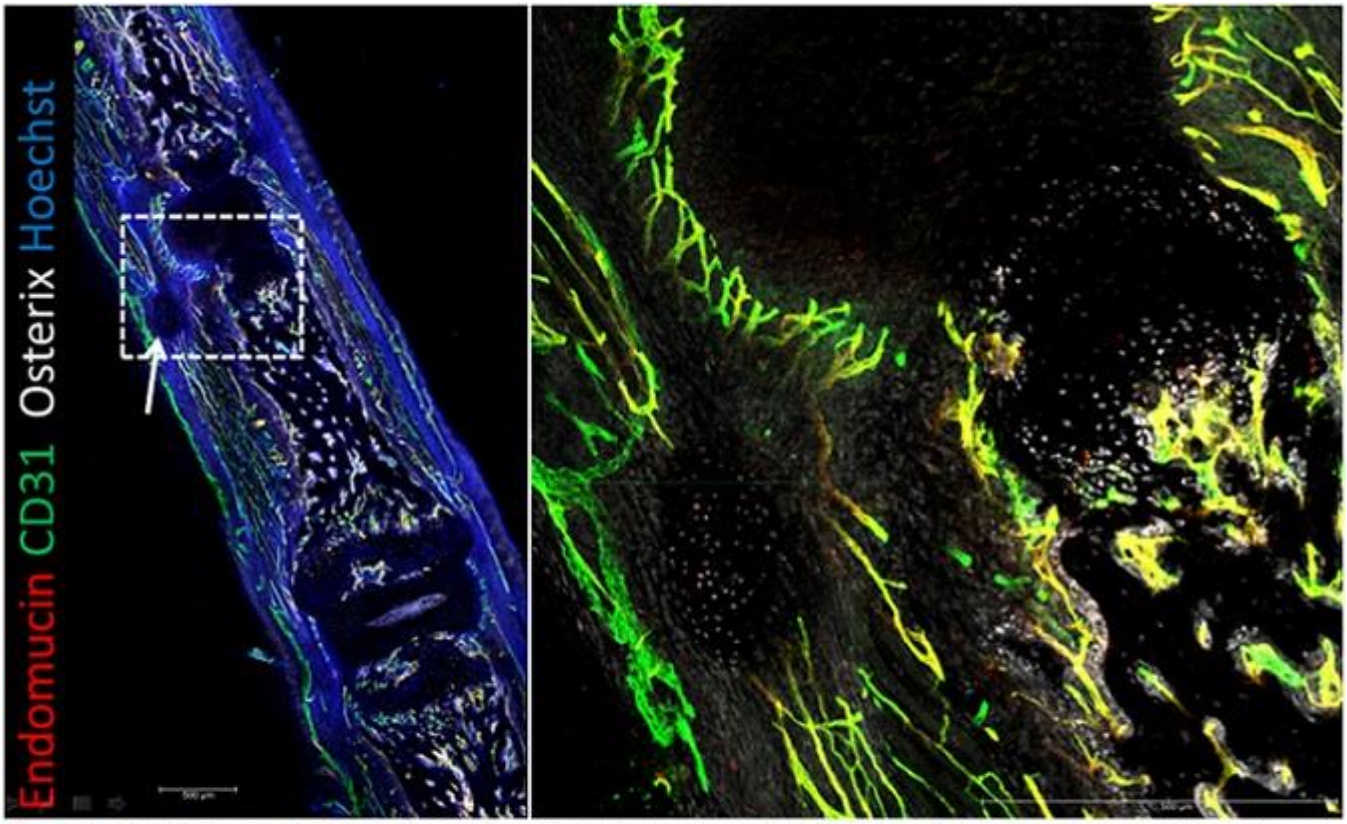

Figure 1. Type H vessel association with ectopic bone formation in 6-week-old murine vertebra. Left panel: Confocal tile scan of tmTNF tg vertebrae showing $endomucin^+$ (red), which labels all vessels except arteries, and $CD31^+$ (green) endothelial cells. Osterix (white) labels osteoprogenitors and nuclei are labeled by Hoechst (blue). Right panel: Higher magnification of $osterix^+$ osteoprogenitors at ectopic location. $Osterix^+$ cells are found around type H ($CD31^{hi}endomucin^{hi}$) vessels.

P_28

Lipid profile and cardiovascular risk in subjects at risk for rheumatoid arthritis

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Background

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease associated with an increased cardiovascular (CV) risk that is already present at the time of diagnosis. However, it is unclear at what point in the period before diagnosis of RA the CV risk increases. Therefore, we assessed the 10-year risk of CV morbidity and mortality in a cohort of subjects at risk for RA and analyzed associations with anti-citrullinated protein antibody (ACPA) status and arthritis development.

Methods

In a cohort of 555 consecutive arthralgia patients with positivity for rheumatoid factor (RF) and / or ACPA, demographics, medical history, medication use and comorbidities were assessed. Lipid profile was determined and blood pressure was measured in a subset of patients. The 10-year CV risk score according to the Dutch CV risk management guideline (Dutch Systematic Coronary Risk Evaluations (SCORE)) was calculated for patients of whom data were complete.

Results

ACPA positive subjects (n=348) were younger (mean age 48.3 vs 51.5, p=0.002), had higher CRP levels (median 2.3 mg/l vs 2.0, p=0.007) and had lower cholesterol (mean level 5.2 mmol/l vs 5.6, p<0.001), HDL (mean level 1.0 mmol/l vs 1.2, p<0.001) and LDL levels (mean level 3.5 mmol/l vs 3.7, p=0.021) than ACPA negative subjects. Subjects who developed arthritis (n=188) had a higher heart rate (67.6 beats per minute vs 63.3, p=0.048), lower cholesterol (mean level 5.2 vs 5.5, p=0.006), HDL (mean level 1.0 vs 1.1, p=0.003) and ApoB levels (mean level 0.8 g/l vs 0.9, p=0.011) compared to subjects who did not develop arthritis.

The Dutch SCORE was calculated in 144 subjects (median 2, IQR 1-9). 75.7% had a low risk (SCORE<10%), 11.8% a medium risk (SCORE 10-<20%) and 12.5% had a high 10-year risk (SCORE>20%) of cardiovascular morbidity and mortality. The score was not associated with ACPA status or arthritis development.

Conclusion

Similar lipid abnormalities as known in RA patients with untreated disease were also present in seropositive arthralgia patients at risk for RA. However, arthralgia subjects who developed arthritis did not have a higher CV risk score than those who did not develop arthritis. Also, despite differences in lipid profile, the CV risk score does not differ between ACPA positive and ACPA negative subjects at risk for RA. Overall, differences in lipid profile were too small to have an effect on the 10 year risk of CV morbidity and mortality as calculated by the Dutch CV risk score.

P_29

Lymphatic endothelial cells amongst other stromal cell subsets have unique properties to shape peripheral T cell responses

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Background

Psoriatic arthritis is a destructive joint disease developing in approximately 30% of psoriasis patients. Both psoriasis and psoriatic arthritis are T-cell mediated diseases, but how T cells migrate from the skin to joint is unclear. Growing evidence suggests that a defective lymphatic system and the lymphatic endothelial cells (LECs) might play a crucial role in the progression of psoriasis to psoriatic arthritis.

Objective

In this study, we aim to elucidate the role of the lymphatic system in psoriasis and psoriatic arthritis. We hypothesize that healthy LECs have immunoregulatory properties that are lost in psoriatic arthritis allowing transmission of pathogenic T cells from the skin to the joints.

Methods

Human dermal LECs ($CD31^+$ $podoplanin^+$) and fibroblasts ($CD31^-$$podoplanin^-$) were isolated from skin from healthy individuals undergoing elective surgery. Human lymph node LECs ($CD31^+$ $podoplanin^+$) were isolated from patients undergoing vascular surgery excluding patients with psoriasis or any rheumatic disease. Expression of immunoregulatory molecules was analyzed by flow cytometry and RT-qPCR.

Results

Healthy human dermal LECs and healthy human lymph node LECs express immunoregulatory and costimulatory molecules, such as programmed death-ligand 1 (PD-L1), galectin 9, glucocorticoid-induced TNFR-related ligand (GITRL) and OX40 ligand. Furthermore, both LECs from lymph node and skin as well as skin BECs are $HLA\text{-}DR^+$ in contrast to healthy dermal fibroblasts and healthy synovial fibroblasts.

Conclusion

Both dermal and lymph node LECs are HLA-DR+ and express several immunoregulatory and costimulatory molecules indicating an important role for LECs in shaping peripheral T cell responses. Further studies involving dermal, lymph node and synovial LECs from psoriasis and psoriatic arthritis patients are underway.

P_30

Impact of Time to Minimal Disease Activity and Quality of Life one year after diagnosis of Psoriatic Arthritis

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Background

From previous cross-sectional research we know that minimal disease activity (MDA) is associated with better health-related quality of life (HRQoL) in psoriatic arthritis (PsA). Whether being in MDA early is related to better outcomes is unknown.

Objective

We aimed to evaluate the impact of time to MDA on HRQoL at one year follow up in patients newly diagnosed with PsA.

Methods

Data collected in the Dutch southwest early PsA cohort (DEPAR) study was used. PsA patients with a new diagnosis of PsA and not yet treated for PsA with disease-modifying antirheumatic drugs are eligible to participate. MDA status was determined every three months in the first year by trained research nurses. Short Form 36 (SF36) Physical Component Scores (SF36-PCS) and Mental Component Scores (SF36-MCS) were used to assess HRQoL.

Results

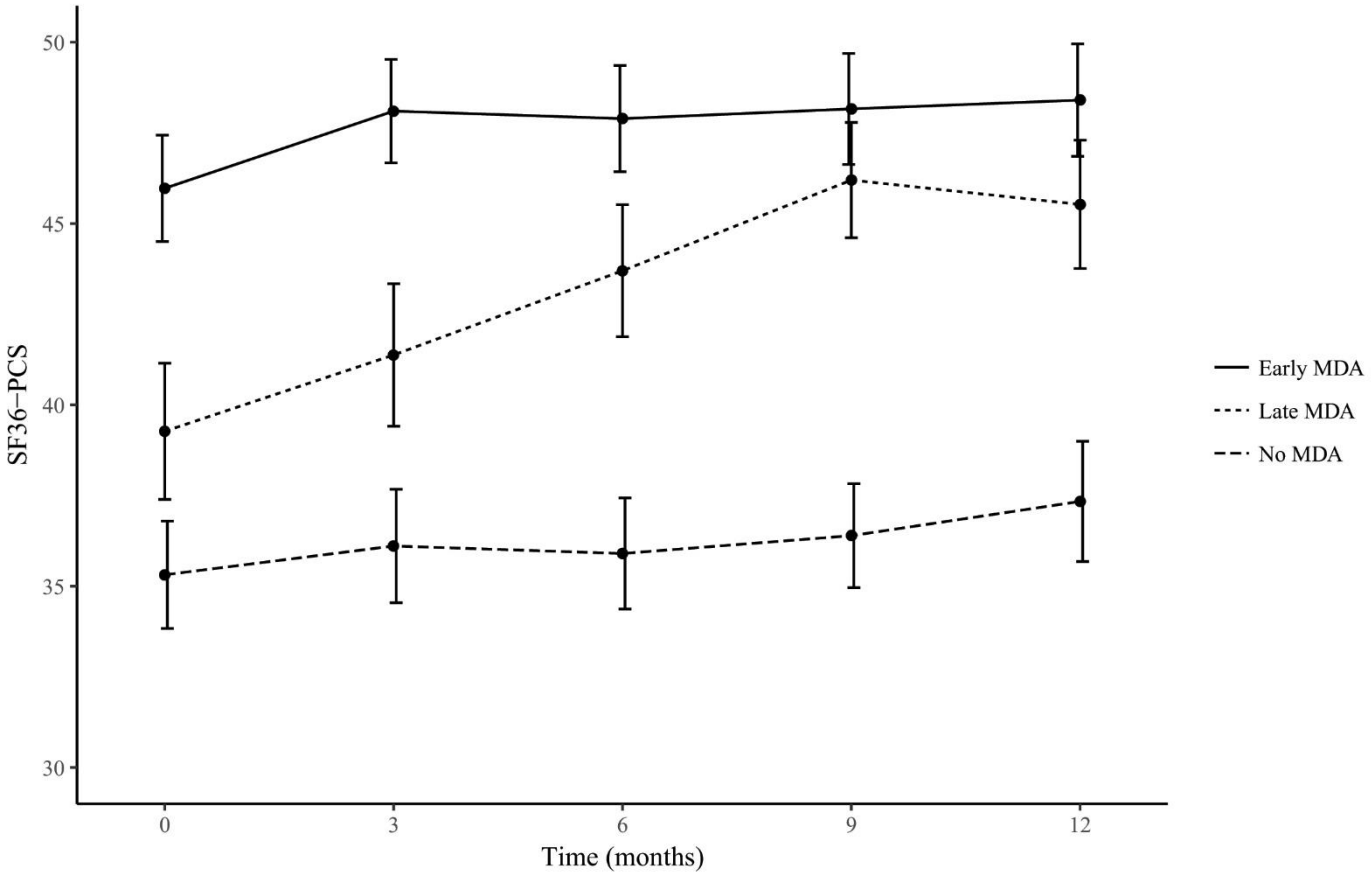
In July 2017, 296 patients had had their 1-year visit (mean age 51 years, 53% male). Of those, 96 (32%) were in MDA within three months (early MDA), 78 (26%) between 3 and 12 months (late MDA), 98 (33%) were not in MDA at any time during the first year (no MDA) and 24 (8%) patients could not be assigned to either group due to missing data. 43 early MDA patients (46%) had sustained MDA and 46 (60%) of the late MDA patients. Late MDA patients and no MDA patients had significantly higher baseline tender joint counts, enthesitis scores, and VAS scores than early MDA patients. Methotrexate was also prescribed more frequently in no MDA (81%) and late MDA (79%) groups than early MDA (62%). At baseline SF36-PCS scores were significantly lower in the late and no MDA groups, but after one year only the scores of the no MDA group were significantly lower (Figure 1).

Conclusion

HRQoL of early MDA patients and late MDA patients did not differ significantly at twelve months, but patients not in MDA in their first year after diagnosis had significantly worse HRQoL than patients that are in MDA. A quarter of patients was in MDA within three months and in total 58% within the first year.

Figure 1. SF36-PCS scores in MDA groups over first year follow up

Figure 1. SF36-PCS scores in MDA groups over first year follow up



SF36-PCS: Short-Form 36 Physical Component Summary; MDA: Minimal Disease activity; Early MDA: MDA within three months; Late MDA: MDA within three to twelve months; No MDA: no MDA in first year. Data shown as mean with 95% Confidence Intervals.

P_31

Corticosteroid bridging strategies with methotrexate monotherapy in early rheumatoid and undifferentiated arthritis; a comparison of efficacy and toxicity in 2 clinical trials

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Background

Should we start with high or low dose glucocorticoid (GC) bridging therapy in early arthritis?

Objectives

To compare short term clinical efficacy of high and low dose GC tapering schedules with MTX monotherapy in 2 clinical trials.

Methods

In trial A, early RA and UA (arthritis in ≥1 joint(s), <1 year symptoms) patients were randomised to 3 different treatment arms. Here we used data of arm C where patients were treated with prednisone (15 mg/day, tapered to 0 in 10 weeks) and MTX (25mg/week). In trial B, RA and UA (arthritis in ≥1 joint and ≥1 other painful joint) patients were treated with prednisone (60 mg/day, tapered in 7 weeks to 7.5 mg/day, continued to 4 months) and MTX (25 mg/week). We compared changes in DAS and HAQ and percentages with DAS≤2.4 and with DAS<1.6 at first evaluation (3 months in trial A, 4 months in trial B). After multivariate normal imputation we applied generalized estimating equations (GEE) for linear outcomes and logistic regression models for binary outcomes, adjusted for potential baseline confounders (figure 1). Adverse events were compared using binominal probability test.

Results

At baseline, patients in trial A (n=97) were more often APCA positive (77% vs 56%) and less often had UA (2% vs 20%) than in trial B (n=610). Baseline DAS, HAQ and symptom duration were comparable.

At the first evaluation time point (median 3.0 (IQR 2.98-3.2) months in trial A, 4.0 (3.8-4.2) in trial B), DAS and HAQ had decreased significantly less in trial A (DAS β 0.500 (95% CI 0.276; 0.725), and HAQ 0.330 (0.189; 0.470) (figure 1). Fewer patients in trial B achieved DAS<1.6 (29% vs 63%) (adjusted OR 0.215 (95% CI 0.124; 0.373) and DAS≤2.4 (56% vs 81% (adjusted OR 0.249 (0.143; 0.435)). Presence of ACPA was positively associated with achieving DAS<1.6 in trial B, but not in trial A. Per 100 patient years, 23 serious adverse events were reported in trial A and 8 in trial B (table 1).

Conclusion

In early arthritis patients, MTX with prednisone 60 mg/day tapered in 7 weeks to and continued at 7.5 mg/day was associated with better early clinical outcomes and fewer serious adverse events but more hypertension and hyperglycaemia than MTX with prednisone 15mg daily tapered to nil in 10 weeks.

Image/graph

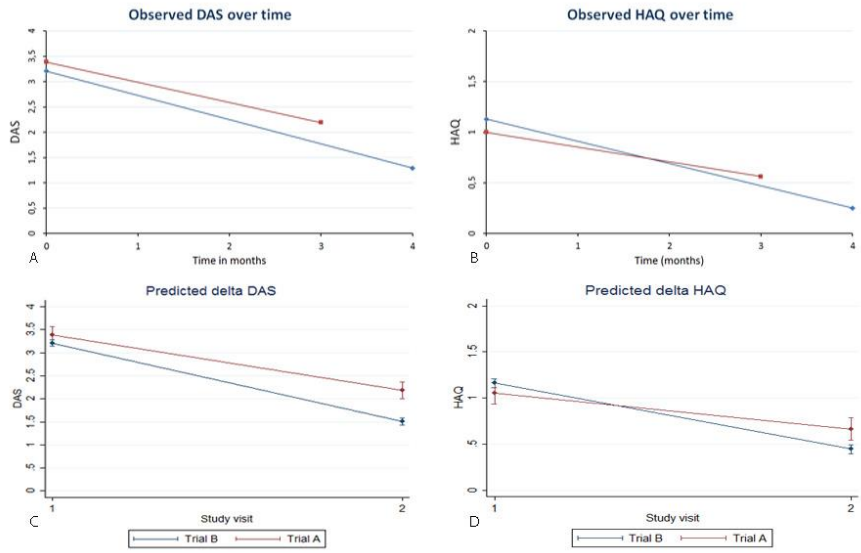

Figure 1A: Observed DAS over time, B: Observed HAQ over time, C: Predicted delta DAS, D: Predicted delta HAQ. All predictions are from multiple imputed models, adjusted for age, gender, body mas index, presence of ACPA, presence of rheumatiod factor, symptom duration, effect over time (in GEE) and baseline DAS (for binary outcomes). DAS, Disease Activity Score; HAQ, Health Assesment Questionnaire.

Table 1. Most frequently reported adverse events, per 100 patient years

	Trial A (n=97)	Trial B (n=610)	p
Malaise	42.9	9.45	0.000
Gastrointestinal symptoms	97.6	48.7	0.004
Hypertension	0.00	9.95	0.091
Hyperglycemia (>7.8mmol/l)	0.00	8.46	0.130
Infections	46.9	39.8	0.582
Skin rashes	27.3	7.96	0.014
Hair loss	23.4	9.45	0.074
Headache	31.2	8.95	0.008
Depression/feeling sad	31.2	11.9	0.031
Bone marrow depression	15.6	0.00	0.000
High creatinine (above normal)	11.7	0.00	0.001
Liver enzymes (above normal)	35.1	22.4	0.229
Dizziness	3.90	5.47	0.837
Dyspnea	0.00	3.48	0.432