O_01

U-Act-Early trial 3 years follow-up. Longer-term effectiveness of treat-to-target strategies in early RA with tocilizumab, methotrexate, or their combination

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Background

The U-Act-Early trial was a 2-year placebo-controlled, double-blind randomized controlled trial in early (DMARD-naïve) RA patients treated to the target of sustained remission (SR), starting with tocilizumab (TCZ), methotrexate (MTX) or their combination (TCZ+MTX)[1]. When the target was achieved, medication was tapered and stopped, if patients remained in remission. During the trial, the strategies starting with TCZ were more effective than the strategy initiating MTX only. Subsequently, patients were followed for 3 years, during which treatment was open and according to usual care.

Objective

To establish the effectiveness of step-up strategies starting with MTX, TCZ or their combination in early RA over a 5 year period.

Method

226 of the 317 patients starting in the U-Act-Early trial (initial strategy: 75 TCZ+MTX, 79 TCZ, 72 MTX) participated in the 3 year follow-up phase. DAS28 was collected every 3 months during the first year and every 6 months thereafter. The primary endpoint was SR, defined as DAS28<2.6 and 28 joint count ≤4 for >24 weeks. Secondary endpoints were sustained drug-free remission (sDFR), defined as remission for ≥3 months after tapering and stopping all medication during SR, and DAS28 over 5 years. Differences between the randomized strategies in proportions of patients achieving SR and sDFR and in durations of these endpoints were tested. A mixed model analysis was used to compare DAS28 over time, with random intercept and fixed effects for: treatment, visit-week, interaction visit-week*treatment, and corrections for gender, age, and for DAS28, RA-duration, CRP and RF-positivity at baseline.

Results

Baseline characteristics at start of U-Act-Early of the patients included in this 3 year follow-up study were not significantly different from those of all patients included in U-Act-Early trial. Over 5 years, SR was achieved in 224/226 (99%) patients without significant differences (p=0.15) between the initial strategies in proportions of patients achieving it, nor in durations (p=0.96) of these endpoints, Table 1. Neither between-group significant differences were found for sDFR (proportion; p=0.10, duration; p=0.27). The mean DAS28 over 5 years was not significantly different between initial strategies (TCZ+MTX vs. MTX;p=0.32, TCZ vs. MTX;p=0.36), Figure 1.

Conclusion

On the short-term, initiation of TCZ-based strategies yields the most benefit, but on longer-term, no difference in important clinical outcomes was found anymore between initial strategies. Almost all patients achieved SR over 5 years, with a tendency for longer duration of sDFR in the TCZ+MTX strategy.

References

[1]Bijlsma JWJ, et al. *Lancet.* 2016;388;343-55

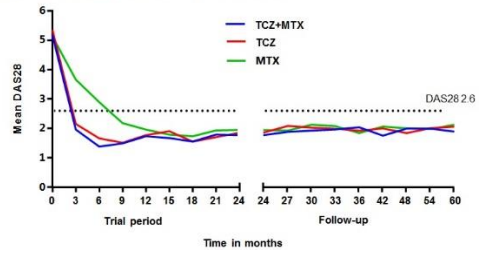
Table 1

Table 1 Outcome for sustained (drug free) remission over 5 years

	Initial treatment strategy group			
	TCZ+MTX	TCZ+placebo	MTX+placebo	p-value
Sustained remission				
Proportion achieving, n/N (%)	75/75 (100)	77/79 (97.5)	72/72 (100)	0.15[1]
Duration weeks, Median (IQR)	49 (37 - 81)	52 (40 - 71)	46 (36 - 114)	0.96[2]
Sustained drug free remission				
Proportion achieving, n/N (%)	26/75 (34.7)	19/79 (24.1)	14/72 (19.4)	0.10[1]
Duration weeks, Median (IQR)	106 (72 - 157)	83 (31 - 156)	71 (30 - 147)	0.27[2]

[1]= Cochran-Mantel-Haenszel test, [2]=Kruskal-Wallis test

Figure 1 DAS28 over time stratified for initial treatment strategy



O_02

Gradual tapering TNF blockers versus conventional synthetic DMARDs in patients with Rheumatoid Arthritis in sustained remission: first year results of the randomised controlled TARA-study

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Background
Current guidelines recommend to consider tapering treatment in patients in sustained remission, but an optimal approach to gradually de-escalate conventional synthetic or biologic DMARDs (respectively csDMARDs and bDMARDs) is currently lacking.
Objective
The aim of this study is to evaluate the effectiveness of two tapering strategies, namely gradual tapering of csDMARDs and anti-TNF therapy during one year of follow-up.
Methods
In this multicenter single-blinded randomised controlled trial RA patients in sustained remission for at least 3 consecutive months, defined as a DAS≤2.4 and a swollen joint count (SJC) ≤1, which was achieved with csDMARDs and a TNF blocker were included. Eligible patients were randomised into gradual tapering csDMARDs followed by the TNF blocker or vice versa. Medication was gradually tapered in three steps over the course of 6 months: first cutting the dosage into half, a quarter and thereafter it was stopped. The primary outcome was disease flare defined as DAS>2.4 and/or SJC>1. Secondary outcomes were quality of life and functional ability.
Results
A total of 189 patients were randomly assigned to tapering csDMARDs (n=94) or tapering anti-TNF (n=95). Patients had an average symptom duration of 6.7 years and were predominantly female (66%) with an average age of 56.6 years (Figure 1A). The cumulative flare ratio in the csDMARD and anti-TNF tapering group was respectively 35% and 45% (Figure 1B), which corresponds with a hazard ratio of 0.91 (95% CI, 0.68-1.22, p=0.55). In 48% and 51% of patients respectively tapering csDMARDs or anti-TNF the medication could be completely withdrawn (Figure 1C). Furthermore, mean DAS and mean HAQ over time, and after 1 year, did not differ between both tapering groups (Figure 1D and E).
Conclusion
There were no significant differences in flare ratios, disease activity and functional ability between both tapering strategies during the first year of follow-up. Therefore, in RA patients who are in sustained remission we advise to taper anti-TNF first, but before tapering therapy rheumatologists should take the risk of a disease flare and patient's wishes into account.

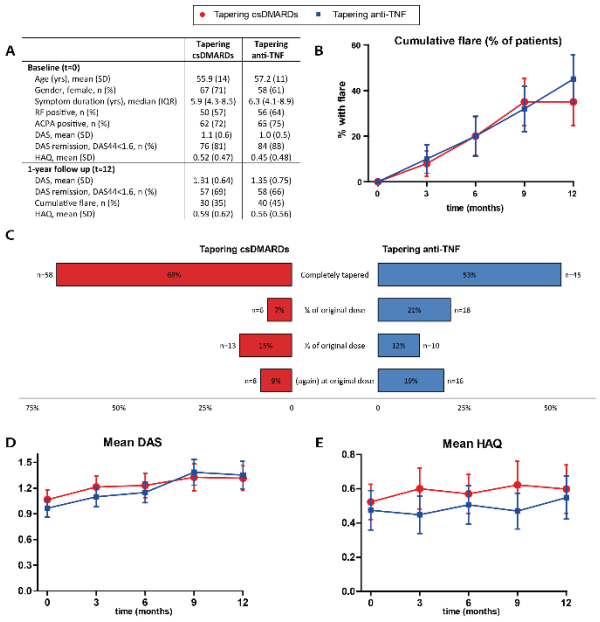

Figure 1 (A) Baseline characteristics and results after 12 months of follow-up of both tapering groups. (B) Cumulative flare over time, error bars indicate 95% confidence intervals. (C) Treatment at 12 months. Columns indicate the percentage of patients that tapered medication until the indicated amount of the original dose. (D) Mean DAS over time, error bars indicate 95% confidence intervals. (E) Mean HAQ over time, error bars indicate 95% confidense intervals. Abbreviations: ACPA; anti-citrullinated protein antibody, csDMARDs; conventional synthetic DMARDs, DAS; disease activity score, HAQ; health assessment questionnaire, RF; rheumatoid factor.

O_03

Serum drug concentrations to optimise switching between biologic agents in rheumatoid arthritis

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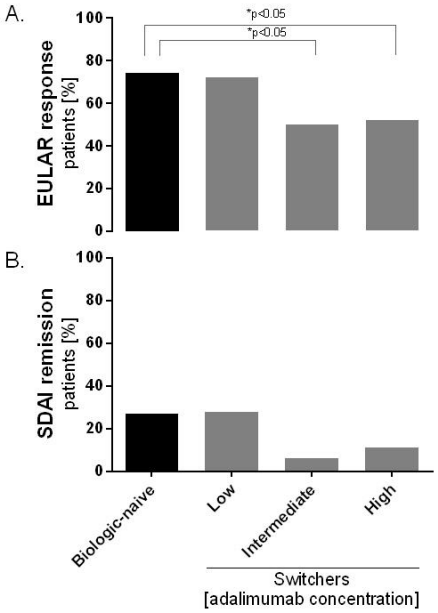
Background
Inadequate response to adalimumab can be caused by insufficient blockade of the target tumor necrosis factor (TNF) at low serum concentrations. In such cases, patients may respond to another TNF inhibitor.
Objectives
To investigate whether the serum adalimumab concentration is related to the efficacy of a second TNF-inhibitor, etanercept, in rheumatoid arthritis (RA).
Methods
Consecutive patients with RA (n=449) treated with etanercept were followed in the Reade Rheumatology Registry, an observational cohort (NTR no.6868). Patients received etanercept 50 mg weekly or 25 mg twice a week. In patients previously on adalimumab 40mg every other week (switchers, n=69), serum concentrations were determined prior to treatment discontinuation with an enzyme linked immunosorbent assay. According to the adalimumab concentration three subgroups were formed; <0.5 µg/mL (n=18); 0.5-5.0 µg/mL (n=18); >5.0 µg/mL (n=27). ADAs were measured using the antigen binding test. Switcher-subgroups were compared with patients starting etanercept without prior biologic agents (biologic-naive; n=380).Clinical endpoints were percentage of patients achieving European League Against Rheumatism (EULAR) good or moderate response; the Simplified Disease Activity Index remission criteria (SDAI<3.3); and the mean change in disease activity score of 28 joints (DAS28) after 52 weeks.
Results
Median (IQR) adalimumab concentration of the three switcher-groups were respectively 0.0 µg/mL (0.0-0.05), 2.5 µg/mL (1.5-4.3) and 7.4 µg/mL (6.0-11.8). ADAs were detected in 16/18 patients with concentration <0.5 µg/mL, 6/18 patients with concentrations between 0.5-5.0 µg/mL and 3/27 patients with concentration >5.0 µg/mL. Response rate of switchers with adalimumab concentrations <0.5 µg/mL was comparable to biological-naïve patients whereas switchers with concentrations between 0.5-5.0 µg/mL and >5.0 µg/mL responded less often regarding EULAR response criteria (respectively 74%, 72%, 50% and 52%;**Figure A**) and SDAI remission (respectively 27%, 27%, 6%, 11%;**Figure B**). Mean (± standard deviation) change in DAS28 after 52 weeks compared to baseline was 1.6±1.4 for biologic-naive patients; 1.6±1.6 for switchers with concentrations <0.5 µg/mL; 0.5±1.8 for switchers with concentrations between 0.5-5.0 µg/mL; and 0.9±1.2 for switchers with concentration >5.0 µg/mL.
Conclusion
We showed that patients with an inadequate response to adalimumab, in the presence of sufficient drug concentrations, benefit less from switch to another TNF inhibitor. Measuring serum drug concentrations in adalimumab inadequate responders may guide subsequent therapy.



O_04

Is there a potential for therapeutic drug monitoring of subcutaneous tocilizumab in patients with rheumatoid arthritis in daily practice?

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Background

Tocilizumab (TCZ), is a humanized antibody that competitively inhibits membrane-bound and soluble IL-6 receptors. Subcutaneous (sc) TCZ might be a potential candidate for therapeutic drug monitoring (TDM) since a high variability in serum concentrations has been reported. Considering that TCZ concentrations above 1 µg/mL have been claimed to be sufficient for normalizing CRP production (1), there might be an overexposure in a substantial proportion of patients. We expect that patients can at least reduce to a dose aiming for a trough concentration of 5 µg/mL. Insights in serum concentrations of sc TCZ with clinical efficacy are lacking, but are necessary to reduce overexposure, potential dose-dependent adverse effects and at the same time reduce costs.

Objectives

To describe TCZ trough serum concentrations in patients with rheumatoid arthritis (RA) treated with sc TCZ.

Methods

Prospective study with consecutive RA patients starting treatment with sc TCZ between June 2015 to October 2017 who had previously failed treatment with at least two DMARDs, including MTX. TCZ was administered at a dose of 162 mg every week and patients were followed for 28 weeks. The study was conducted at the Amsterdam Rheumatology and Immunology Center | Reade. Serum trough samples were collected at baseline and at 4, 16, 28 weeks thereafter. An enzyme-linked immunosorbent assay (ELISA) was used for TCZ measurement. To analyze the concentration variability among patients at 28 weeks, a last observation carried forward approach was used.

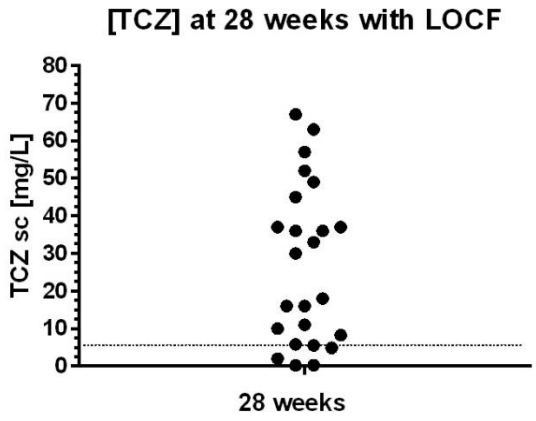
Results

In total, 26 patients were included in the study and 94 TCZ serum concentrations were measured. Median and interquartile range (IQR) of the follow-up period was 28 (16-28) weeks and 54% of the patients accomplished week 28. Drug concentrations ranged from 0.2 to 63 µg/mL, with an overall median (IQR) of 26,0 (10,5-42,0) µg/m. In the majority of patients, TCZ concentrations stabilized after 4 weeks of treatment. Variability in drug concentrations at 28 weeks is shown in figure 1. Median (IQR) TCZ serum concentrations at 28 weeks was 24,0 (6.4-43,0) µg/mL, 92% of the patients achieved a concentration above 1 µg/mL and 88% had a concentration > 5 µg/mL.

Conclusions

The Interindividual variability among patients on sc TCZ is remarkably high. The majority of the patients achieved serum concentrations far above 5 µg/mL, suggesting overexposure in those patients. Therefore, TDM might be useful to optimize treatment, reduce (potential) side effects and achieve cost-effectiveness.

Figure 1: TCZ concentration in RA patients after 28 weeks.



O_05

Finding the optimal treatment strategy for disease activity-guided dose reduction of adalimumab and etanercept in rheumatoid arthritis: a modelling study

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Background

Several studies have shown that disease activity-guided dose reduction without deterioration of disease activity is possible, while saving costs in patients with rheumatoid arthritis and stable and low disease activity[1]. Despite these positive results, questions remain on the optimal tapering strategy. Different strategies are conceivable, with varying results regarding the balance between number of flares, utilities and costs.

Objective

The objective of this study was to investigate the most cost-effective TNFi dose reduction strategy for RA patients using a modelling design.

Methods

In a cost-utility analysis using Markov modelling based on data from the DRESS study[2], STRASS study[3], and the RA Nijmegen cohort, the following strategies were tested against continuation: 1. Four-step DRESS tapering (figure 1: 100%-67%-50%-0%); 2. Tapering with an extra dosage step of 33%; 3. Tapering without withdrawal; 4. Use of a stricter flare criterion (DAS>2.6); and 5. Use of a predictor (biomarker: 80% specific, 80% sensitive, €100 per test) for successful tapering. Scenario analyses with 30% and 50% drug price discount and no discounting were executed. Also, it was examined how well a biomarker should be able to predict to become cost-effective compared to the other strategies.

Results

All examined tapering strategies were found to be cost saving but yielded more short-lived flares compared to continuation (table 1). The change in utilities was minimal and not clinically relevant. Strategy 1 was cost-effective compared to all other strategies (highest incremental Net Monetary Benefit (iNMB)). However, there was a large overlap in credible intervals, especially between strategy 1 and 2. Scenario analyses showed that 50% reduction of drug prices would result in the highest iNMB for strategy 2. A biomarker only becomes cost-effective when it has a sensitivity and specificity of at least 86%.

Conclusion

All dose reduction strategies dominated the continuation strategy regarding cost-effectiveness. Because our study showed a comparable iNMB for tapering in four or five steps, we recommend a choice between these strategies, based on shared decision making.

References

[1]Nam JL et al, Ann Rheum Dis. 2017 Jun;76(6):1113-1136

[2]Van Herwaarden et al, BMJ. 2015 Apr 9;350:h1389

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Figure 1

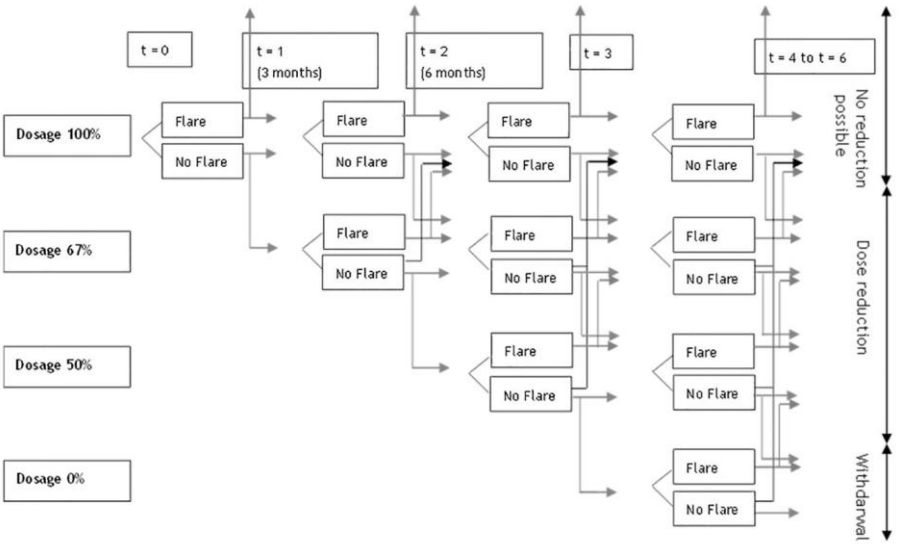

Table 1

Table 1: Main outcomes of each strategy

Outcome measure	0. Continuation (comparator)	1. DRESS strategy (four-step tapering)	2. Five-step tapering	3. No withdrawal	4. Stricter flare criterion	5. Predictor
Costs (€)	21,071 (20,563 - 21,383)	13,198 (12,469 - 13,988)	13,794 (13,150 - 14,496)	14,266 (13,685 - 14,856)	15,943 (15,115 - 16,793)	14,327 (13,281 - 15,359)
QALYs	1.182 (1.165-1.199)	1.177 (1.160-1.193)	1.181 (1.165-1.197)	1.182 (1.166-1.198)	1.189 (1.173-1.205)	1.185 (1.168-1.200)
Mean number of short-lived flares	0.53 (0.35-0.73)	0.97 (0.83-1.12)	0.74 (0.58-0.93)	0.69 (0.52-0.87)	2.08* (1.80-2.41)	0.55 (0.53-0.56)
iNMB**	-	7,434 (6,514-8,302)	7,176 (6,307-8,000)	6,798 (5,977-7,539)	5,650 (3,598-7,625)	6,938 (5,863-8,040)

Data is mean values per patient over 1.5 years (95% credible intervals). *Stricter flare criterion (DAS28 > 2.6). ** NMB = QALYs * WTP/WTA – costs; iNMBs are given at a WTP/WTA of €80,000.

O_06

In rheumatoid arthritis, becoming seronegative over the 1st year of treatment does not translate to better chances of sustained drug-free remission

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Background

In rheumatoid arthritis (RA), it is becoming increasing common to taper or even stop medication, aiming for sustained drug-free remission (SDFR). Baseline autoantibody seropositivity is a poor prognostic factor for this treatment goal. However, autoantibody levels may change and patients may become seronegative under treatment, sometimes termed 'immunological remission'. Understanding how often this occurs and whether it is favorable for achieving SDFR is important to determine whether becoming seronegative is a meaningful prognostic marker for drug-tapering decisions.

Objective

To longitudinally characterize the levels and presence of autoantibodies in RA patients and to investigate whether changes in these levels and/or presence associates with SDFR.

Methods

In sera of 399 seropositive RA patients in the IMPROVED study[1], we measured, at 4-month-intervals over the first year of treatment: IgG, IgM, and IgA isotypes for anti-cyclic citrullinated peptide-2 (anti-CCP2) and anti-carbamylated protein antibodies (anti-CarP), IgM and IgA for rheumatoid factor (RF), and IgG autoantibodies against 4 citrullinated and 2 acetylated peptides. We investigated whether changes in antibody levels and seroconversion from positive to negative for each individual antibody was favorable for SDFR (drug-free DAS44<1.6 lasting at least one year until last follow-up).

Results

For all 14 antibodies, median levels decreased significantly between baseline and 4 months and then stabilized. Most seroconversion to negative happened within the first 4 months of treatment (with prednisone and methotrexate), after which some patients converted back to seropositive. The prevalence of seroconversion from positive to negative between 0-12 months varied substantially depending on the autoantibody and occurred in 2% (anti-CCP2 IgG) to 66% (anti-CarP IgA) (see Figure). We hypothesized that greater level decreases and seroconversion to negative might be favorable for the long-term outcome SDFR, but surprisingly, greater median decreases in levels were not associated with higher chance of SDFR for any antibody. Furthermore, we found no evidence that rates of SDFR were higher in patients who seroconverted to negative compared to those who stayed seropositive, for any of the 14 antibodies analyzed (see Figure).

Conclusions

Autoantibody levels decrease and seroconversion from positive to negative occurs under treatment, but these changes are not associated with successful drug discontinuation, and are therefore unlikely to be useful biomarkers for treatment decisions in clinical practice.

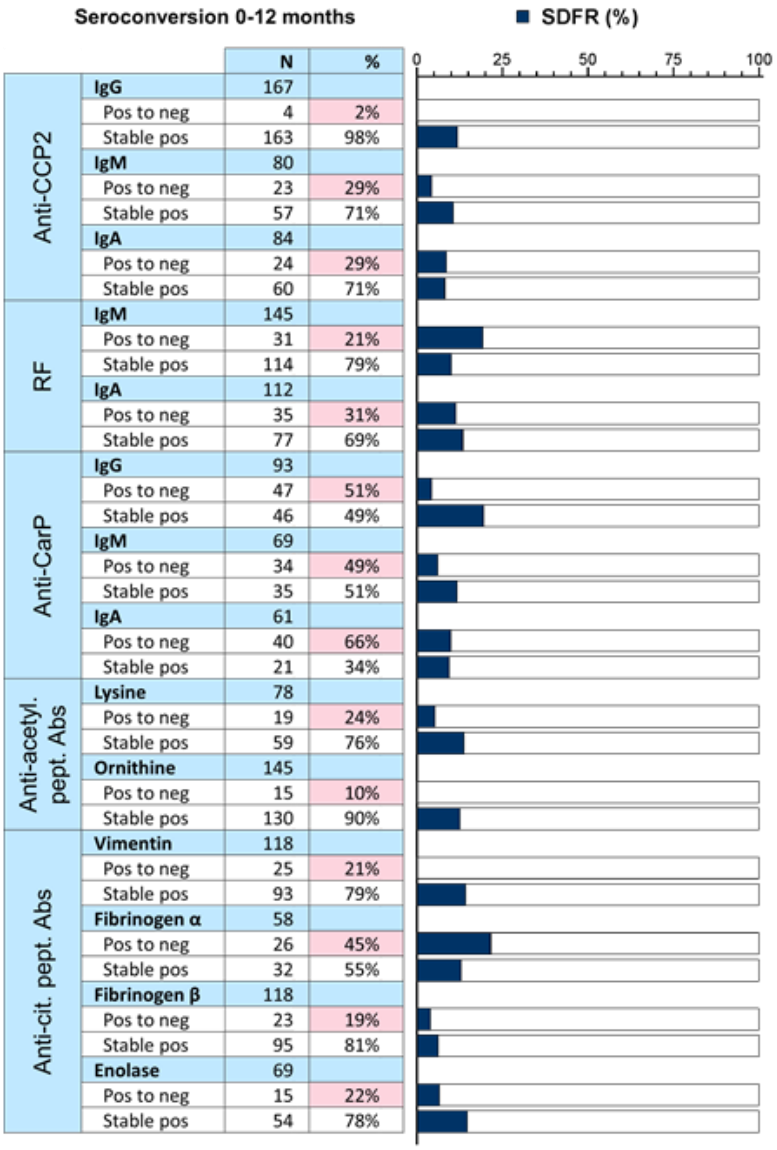

Figure: Percentage of patients reaching SDFR (drug-free DAS44<1.6 lasting ≥1 year until last follow-up), separated by whether patients seroconverted from positive to negative ("Pos to neg") or remained positive ("Stable pos") or for the specified antibody, between 0-12 months.
anti-CCP2 = Anti-cyclic citrullinated peptide-2; RF = rheumatoid factor, anti-CarP = anti-carbamylated protein antibodies; Anti-cit. pept. Abs = anti-citrullinated peptide antibodies; Anti-acetyl. pept. Abs = anti-acetylated peptide antibodies (IgG).

O_07

Is biopsy of the temporal artery still indicated in patients with giant cell arteritis based on clinical grounds and ultrasound of the temporal artery

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Background

Giant cell arteritis (GCA) is the most common systemic vasculitis in patients aged 50 years or older. The diagnosis is usually made on the basis of cranial features, an elevated C-reactive protein and sedimentation rate and an abnormal temporal artery biopsy (TAB). Early diagnosis and rapid initiation of corticosteroids can prevent ischemic complications including permanent visual loss. Different drawbacks of a biopsy are known: a false negative TAB because of sampling error, logistical challenges: a TAB should be performed shortly after the suspicion of GCA because of a decreasing sensitivity of the test under influence of corticosteroids and it is an invasive procedure with the chance of complications.

Objective

To investigate the need for a TAB when the diagnosis GCA can be made on clinical grounds and ultrasound (US).

Methods

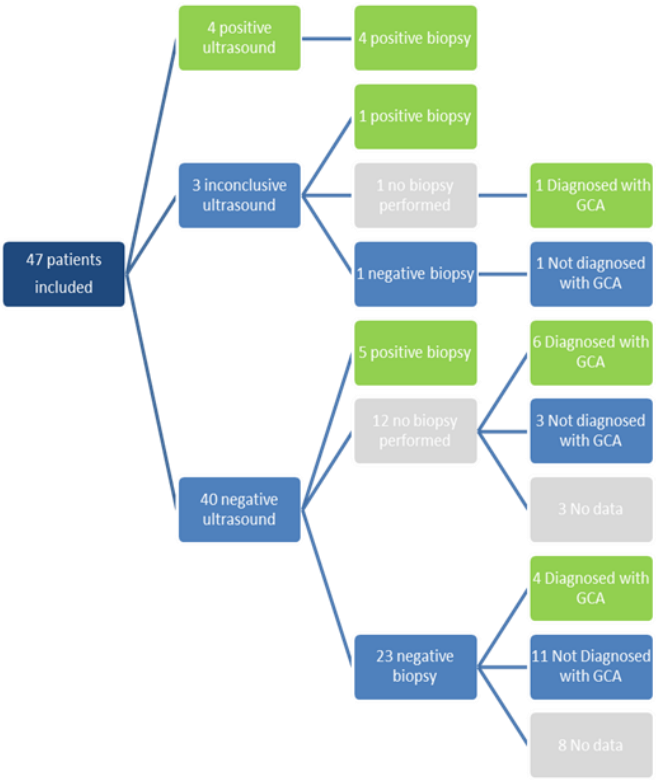
Patients suspected of having GCA underwent US examination of the common superficial temporal just before a TAB was performed. The final diagnosis was made on the basis of the ACR criteria together with the judgment of the treating specialist.

Results

A total of 47 patients suspected of having GCA between june 2012 and june 2017 underwent US. GCA was ultimately diagnosed in 21 (45%) of these patients. In 34 patients a (unilateral) TAB was performed which was positive in 10 cases. The US was positive in 4 patients (8,5%), inconclusive in 3 (6,5 %) and negative in 40 (85%) patients. In the 4 US positive patients the TAB was also positive. In the 3 inconclusive US cases 1 TAB was positive, 1 TAB negative and in 1 case the TAB was not performed. In 4 GCA patients the TAB was negative. In the 40 US negative patients the TAB was positive in 5 cases.

Conclusion

In patients with GCA based on clinical grounds including a positive US a TAB is not necessarily needed.



O_08

Spierechografie: een potentieel nieuw diagnostisch instrument bij idiopathische inflammatoïre myopathieën

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Introductie

Gekwantificeerde spierechografie is een beeldvormende techniek die zich heeft bewezen als een instrument voor het in kaart brengen van pathologie in spierweefsel (1). Daarom onderzochten wij de diagnostische waarde van gekwantificeerde spierechografie bij patiënten verdacht voor idiopathische inflammatoïre myopathie (IIM) en werden resultaten vergeleken met EMG.

Methode

Expert panel diagnose, geblindeerd voor spierechografie, werd gebruikt als gouden standaard bij 57 patiënten met een verdenking op een IIM. De resultaten van gekwantificeerde spierechografie werden volgens een neuromusculair (NMD) algoritme gescoord (normaal/dubieus /afwijkend). De diagnostisch voorspellende waarde van spierechografie en EMG werd geanalyseerd met een 2x2 tabel en multivariate logistisch model.

Resultaten

Tweeëntwintig patiënten (39%) werden gediagnosticeerd met een IIM; 8 polymyositis, 4 dermatomyositis, 4 necrotiserende myopathie, 3 inclusion body myositis en 3 niet specifieke myositis. Zestien patiënten hadden een andere neuromusculaire ziekte.

De IIM groep liet een verhoogde echointensiteit zien van de sternocleidomastoïd, biceps, onderarm flexoren en tibialis anterior. Sensitiviteit, specificiteit, positief en negatief voorspellende waard waren 82%, 51%, 51%, 82% voor spierechografie 63%, 64%, 50%, 75% voor EMG. Multivariate analyse (gecorrigeerd voor leeftijd, serum CK) liet een “area under the curve” (AUC) zien van 0.81 (95% BI 0.69-0.92) voor spierechografie; voor EMG 0.79 (0.67-0.92) en gecombineerd 0.82 (0.70-0.93) (Tabel 1).

Conclusie

Gekwantificeerde spierechografie met neuromusculair algoritme heeft een vergelijkbare diagnostische waarde als EMG. Daarom zou gekwantificeerde spierechografie als instrument kunnen worden gebruikt om te screenen voor myopathieën en om IIM uit te sluiten. Daarbovenop is het een potentieel non-invasief alternatief voor EMG.

O_09

Patients' evaluation of Dutch health care in systemic sclerosis: Unmet needs and preferences

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Background

Systemic sclerosis (SSc) is a chronic autoimmune disease with a large impact on quality of life. To optimize health care, more insight is needed in patients' experiences of the currently provided care.

Objectives

To identify unmet needs and preferences from a patient point of view regarding health care in the Netherlands.

Methods

2093 SSc patients, from both regional (N=7) and university hospitals (N=6) in the Netherlands, were invited through their rheumatologist for an online, anonymous questionnaire comprising multiple choice, multiple response and open questions about health care needs, quality of care and sociodemographic characteristics. Questions, categorized into eight themes, were based on the results of three semi-structured multicenter focusgroup interviews with 23 patients (Table 1).

Results

650 patients (median age 59 years, 75% women) completed the questionnaire at the 21st of February 2018. Median period after diagnosis was eight years, 32% and 20% reported having limited or diffuse cutaneous SSc, respectively. Interestingly, 38% did not know the subtype. 58% received care in an expert center and 39% in ≥2 centers. 30% had to travel > one hour for each visit. Multidisciplinary collaboration was rated 68 out of 100 and information exchange among physicians 66 out of 100. The lack of knowledge about the disease among health professionals (39%, N=249) and difficulty finding experts in SSc (27%, N=171) were most reported hurdles. 10% of patients did not receive any information from their rheumatologist at time of diagnosis, but when provided 97% thought this information was clear. Only 60% (N=390) was referred to a specialized nurse. Although most patients were involved in treatment decisions (84%, N=546), 15% (N=96) did not receive the care they needed in their opinion. During hospital visits, more focus was preferred on fatigue (46%, N=295), Raynaud's phenomenon (32%, N=204), physical disabilities (30%, N=192), impaired hand function (27%, N=177) and coping with the unpredictable course of the disease (24%, N=154). Highest priority was given to improved knowledge among general practitioners (66%) and multidisciplinary collaboration (45%) (Figure 1). Information supply could be improved by creating one national website with clear and reliable information about SSc for both patients and caregivers.

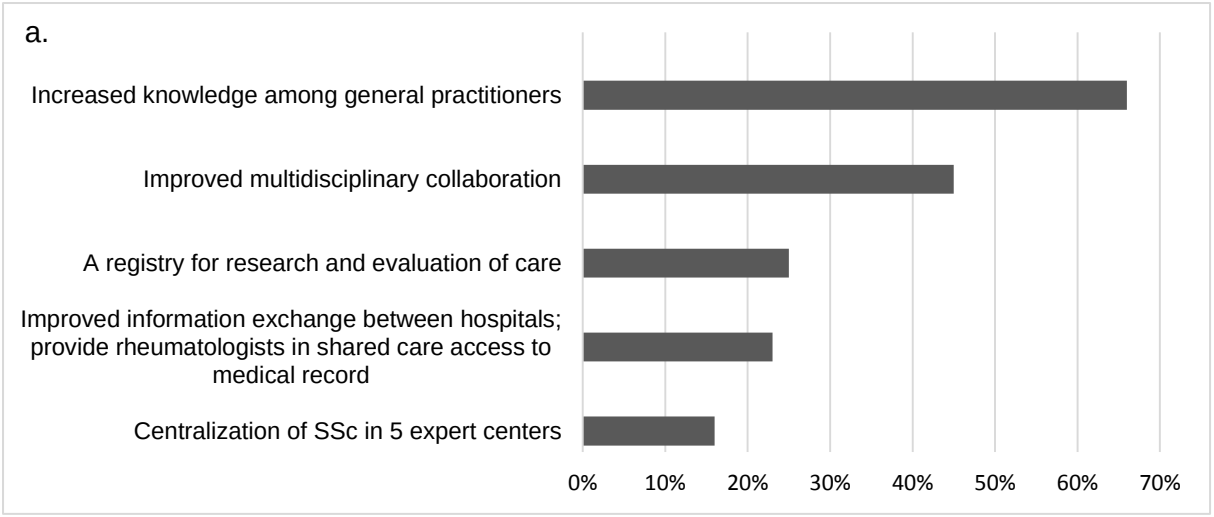
Conclusions

SSc patients prefer more attention to symptoms during doctor's visits and desire improved collaboration, increased knowledge among caregivers and accessible patient education and information. This knowledge will guide the nation-wide initiative to optimize health care for patients with SSc in The Netherlands.

Table 1. Identified health care themes from focusgroup interviews

Themes
Multidisciplinary collaboration
Caregivers education
Information supply
Information exchange among caregivers
Shared care between regional and university hospitals
Organization of health care services
Patient-empowerment
Non-pharmacological support

Figure 1. Top five prioritized points for improvement % (N)
a. On health care in general. b. On information supply. Results from a multi-response question.



b.


One national hub for information for patients and caregivers
Web-based user-interactive question-answering platform for patients and caregivers
Online overview of SSc experts in the Netherlands
Self-management course
Online overview of health professionals in the Netherlands
0%
10%
20%
30%
40%
50%
60%
70%
80%

O_10

What is the effect of cyclophosphamide iv pulse therapy in patients with diffuse cutaneous systemic sclerosis on skin involvement: an observational study

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Introduction: Patients with systemic sclerosis who have proximal skin involvement are classified as diffuse cutaneous systemic sclerosis (DcSSc). Patients with progressive skin involvement have worse prognosis. Treatment options consist among others of cyclophosphamide iv pulse therapy[1]. Recent studies show significant improvement of skin thickening in patients treated with cyclophophamide orally[2], but the effect of cyclophosphamide iv on skin involvement remains unclear.
Objective: To examine the extent of skin involvement during 12 monthly cyclophosphamide iv in DcSSc and to identify factors that predict response to therapy.
Methods: Patients with DcSSc receiving cyclophosphamide iv between 2004 and 2016 were included. Skin involvement was accessed with the modified Rodnan Skinscore (mRSS) at baseline, six, 12, 24 and 36 months by the same trained rheumatologist. Data of baseline and at least one follow-up measurement were included. Missing mRSS data were imputed using multiple imputation by chained equation. Patients were classified as responders if the mRSS decreased at least 5 points and 25% from baseline at month 12. A prediction model for response at 12 months was created using backwards logistic regression considering baseline variables and response at six months as possible predictors.
Results: A total of 99 patients were included. The mean improvement of mRSS over time was -4.05 (95% CI -5.53 to -2.55) (Figure 1). 43% of patients had a response according to the criteria. In univariate prediction models, baseline mRSS (OR 1.06, p=0.024), response at six months (OR: 37.45, P<0.001) and completed treatment (yes/no) (OR: 4.108, p=0.033), were significant predictors of response at 12 months. For the last variable it should be mentioned that some patients who did not achieve a response at month 6 did not continue cyclophosphamide iv for that reason.
Conclusions: This study shows that only 43% of treated DcSSc patients experienced clinical important improvement of skin involvement following cyclophosphamide iv. Response at month 6 is the best predictor for response on month 12. This could imply that at this time point, counseling about other available treatment options, should be considered in those patients.

References:

[1]Kowal-Bielecka O, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Annals of the rheumatic diseases. 2009;68(5):620-8.
[2]Namas R, et al. Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: Post-hoc analyses from the Scleroderma Lung Study I and II. Arthritis care & research. 2017.

	Responders at 12 months (n=40)	Non-responders at 12 months (n=51)
Age, mean (sd)	52 (14)	54 (13)
Female gender, n (%)	19 (48%)	19 (37%)
Baseline mRSS, median (IQR)	19 (15-24)	13 (9-21)
Disease duration (months), median (IQR)	3 (1-12)	6 (2-18)
infusions completed, n (%)		
12	37 (93%)	37 (73%)
=>6 and <12	3 (8%)	14 (27%)
Antibodies		
-ANA	12 (30%)	19 (37%)
-Anti-topoisomerase	24 (60%)	29 (57%)
Response at 6 months	17 (46%)	1 (2%)

Table 1. Demographic and clinical characteristics of responders and non-responders

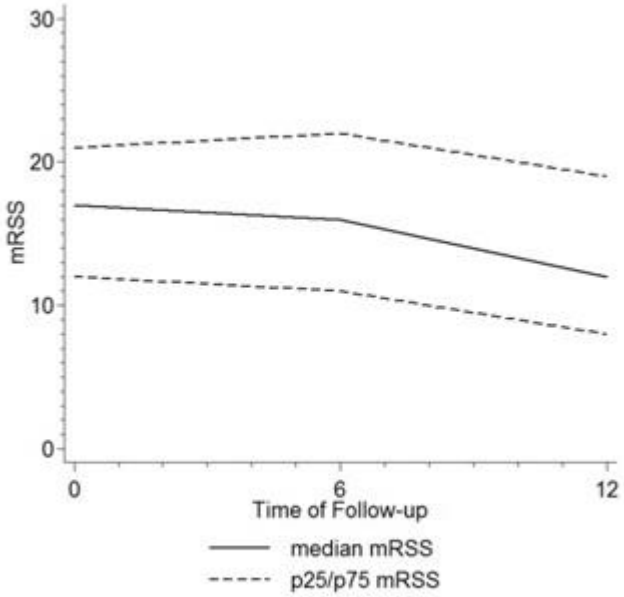

Figure 1. mRSS course of all patients during iv CYC

O_11

Interferon signature might serve as predictive biomarker for development of systemic lupus erythematosus and correlates strongly with Myxovirus-resistance protein A

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Background

Incomplete systemic lupus erythematosus (iSLE) includes a group of patients with typical lupus features, who do not meet classification criteria for systemic lupus erythematosus (SLE). Up to 55% develop established disease, but there are no predictive markers available.(1, 2) Interferon (IFN) type-I is an important early mediator in SLE.(3) The majority of SLE patients show upregulation of interferon-inducible genes. Levels of IFN-related soluble markers, which are easier applicable, are also increased in SLE.(4)

Objectives

To determine IFN signature and IFN-related soluble markers in iSLE patients and compare with SLE patients and controls.

Methods

Thirty iSLE patients (ANA titer ≥1:80, disease duration < 5 years, ≥1 ACR clinical feature), 39 SLE patients with quiescent disease (fulfilling ACR or SLICC criteria, SLEDAI ≤ 4) and 11 healthy controls (HC) were included. RNA was isolated from whole blood using PAXgene tubes, reversely transcribed to cDNA and quantitatively analyzed by Real time PCR.

IFN score was calculated based on cumulative expression of 12 IFN-related transcripts (IP-10, IFI44L, IFIT3, LY6E, MX1, SERPING1, IFITM1, IRF7, STAT1, C1QA, IFI16 and IRF9). An increased IFN-score was defined as > 2 SD of HC. Levels of IFN-related mediators, including IFN-γ induced protein 10 (IP-10) and Myxovirus-resistance protein A (MxA) were measured using ELISA.

Statistical significance between groups was tested with Mann-Whitney U tests. Correlations of continuous data were calculated using Spearman's r test.

Results

Baseline characteristics are shown in Table 1. An increased IFN score was present in 55% of iSLE patients and 46% of SLE patients (p=0.42)(fig 1a).

In iSLE, IFN score correlated positively with ESR (*r*=0.52, p=0.004), SSA titer (*r*=0.64, p=0.02) and cumulative number of ENA (*r*=0.57, p=0.001), and negatively with leukocyte count (*r*=-0.38, p=0.04), Hb (*r*=-0.39, p=0.04), and C4 (*r*=-0.47, p=0.01). SLEDAI, clinical symptoms, nor use of hydroxychloroquine were correlated with IFN score.

Levels of MxA correlated strongly with IFN score in both iSLE (*r*=0.78, p<0.0001)(fig 1b) and SLE (*r*=0.6, p<0.0001). IP-10 levels correlated with IFN score in iSLE (*r*=0.45, p=0.02), but not in SLE.

Conclusions

IFN-signature is present in 55% of patients with iSLE and correlates with ESR, autoantibody number, leukopenia, Hb and hypocomplementemia. Interestingly, MxA levels correlate strongly with IFN-gene upregulation and thus may be a suitable and easily applicable surrogate marker. iSLE patients with IFN upregulation might be at most risk for disease progression; longitudinal data however should be awaited.

Figure 1. (a) IFN score and correlation with MxA

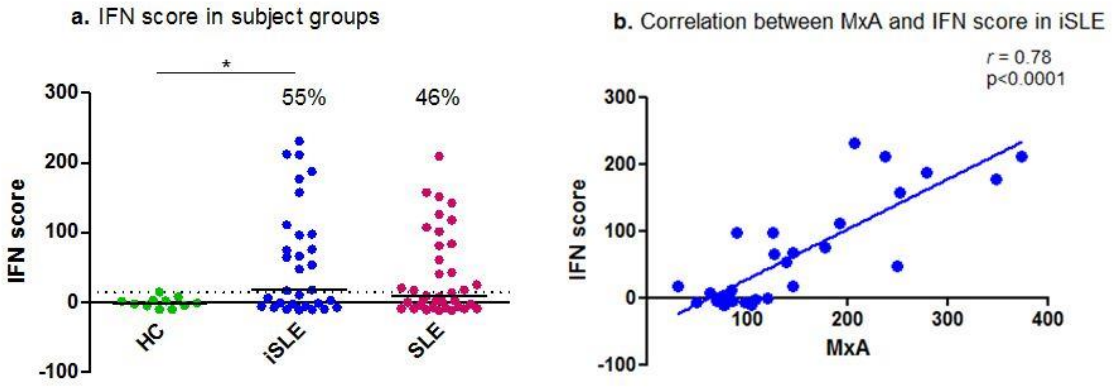

Table 1. Baseline characteristics.

Table 1. Baseline characteristics

	HC (n=11)	**iSLE (n=30)**	**SLE (n=39)**
Female gender , n (%)	10 (91)	25 (79)	32 (82)
Age (median, range)	28 (25-65)	45 (20-83)	41 (19-76)
Disease duration, years median (range)		1.4 (0.1-4.6)	2.7 (0.5-6.8)
ACR criteria, median (range)		3 (1-3)	5 (2-9)
SLICC criteria, median (range)		3 (2-4*)	5 (4-9)
SLEDAI median range)		0 (0-6)	2 (0-4)
Hydroxychloroquine use, n (%)		10 (33)	33 (85)
Immunologic features, n (%)			
ANA or SSA-pattern		30 (100)	39 (100)
Anti-dsDNA		9 (30)	33 (85)
Anti -SSA		14 (47)	12 (31)
Anti-Sm		3 (10)	6 (15)
Decreased complement		4 (13)	26 (67)

*1 patient had 4 immunologic SLICC criteria, but no clinical SLICC criterion

O_12

Treatment strategies aiming at inactive disease in recent onset Juvenile Idiopathic Arthritis: Clinical outcomes of a randomized trial after 24 months

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Background

In rheumatoid arthritis treatment, treatment-to-target has shown to improve disease outcomes including the option of drug tapering and discontinuation. In non-systemic juvenile idiopathic arthritis (nsJIA) this has not been tried in a trial.

Objectives

To investigate which of three treatment strategies, targeting at drug-free inactive disease, is most effective and safe in recent-onset DMARD-naive nsJIA.

Methods

We conducted a randomized, multicenter, single-blinded treatment strategy study with 24 months of follow-up. Patients (oligoarticular JIA, rheumatoid factor negative polyarticular JIA or juvenile psoriatic arthritis) 2-16 years old with symptom duration <18 months were randomized to 1) Sequential DMARD-monotherapy (sulfasalazine (SSZ) or methotrexate (MTX), 2) Combination therapy MTX+6 weeks prednisolone, 3) Combination therapy MTX+ etanercept. Treatment-to-target entailed three-monthly treatment intensifications in case of persistent disease activity. DMARDs were tapered to nil in case of inactive disease for at least 3 (in oligoarticular JIA) or 6 (in polyarticular JIA) months. After 24 months, primary outcomes were time-to-inactive-disease and time-to-flare after DMARD discontinuation. Secondary outcomes were adapted ACRPedi30/50/70/90-scores, functional ability and toxicity. Missing data were imputed. In case of drug-free clinically inactive disease often intentionally no blood was drawn causing non-random missing ESR, and here '0' was imputed for the analysis of inactive disease.

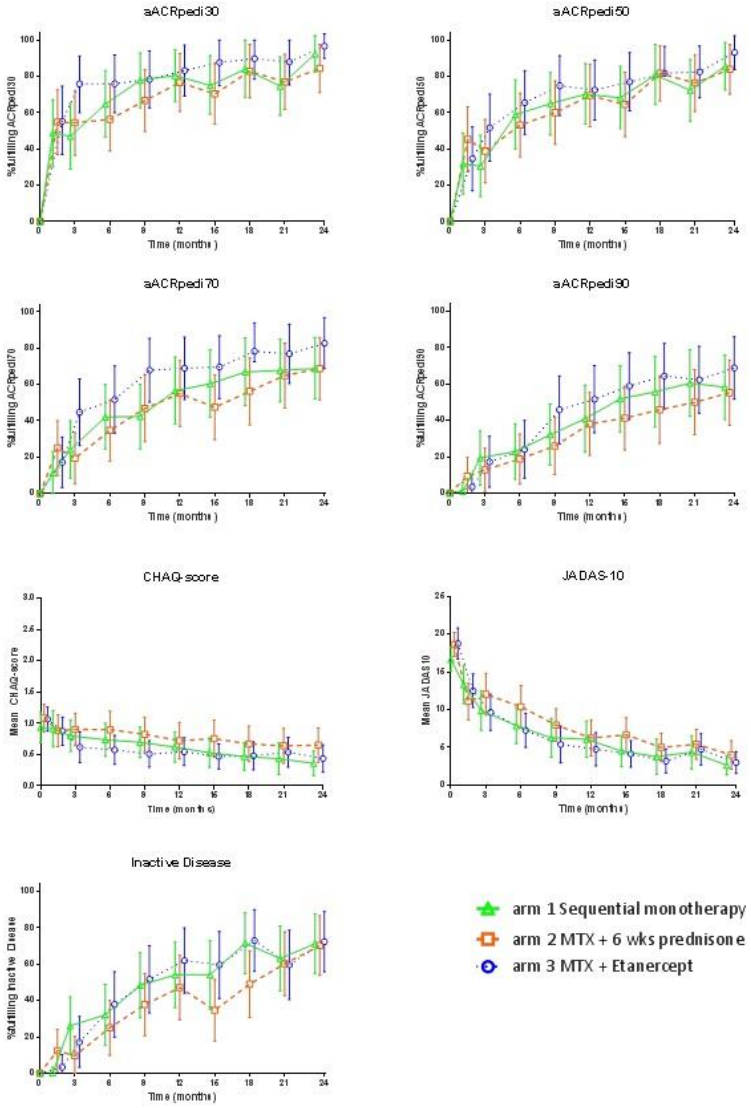
Results

94 children (67% girls) with a median (InterQuartileRange) age of 9.1 (4.6-12.9) years were enrolled: 32 in arms 1 and 2, 30 in arm 3. Eleven had oligo-articular JIA, n=73 polyarticular JIA and n=8 juvenile psoriatic arthritis, 37% were ANA positive. At baseline VAS physician was mean (SD) 49 (16) mm, VAS patient 53 (22) mm, ESR 12.8 (14.7) mm/hr, active joints median 8 (5-12), limited joints 2.5 (1-4.8), and CHAQ-score 1.0 (0.6). After 24 months 71% (arm 1), 69% (arm 2) and 72% (arm 3) of patients had inactive disease and 45% (arm 1) 31% (arm 2) and 41% (arm 3) had stopped all DMARD(s). Time-to-inactive disease (median 9.0 (6.0-12.0) months) was not significantly different between arms, nor was time-to-flare (18.0 (15.0-21.0) months). Adapted ACRpedi-scores were comparably high between arms. Functional ability improved and remained almost normal. Toxicity reports showed mild events in similar rates across all arms.

Conclusions

By treatment to target, inactive disease is a feasible goal in recent onset non-systemic JIA. After 24 months, regardless of initial treatment, inactive disease was reached in over 70% of patients and 39% reached drug-free inactive disease. Tight control seems more important than inducing agent(s).

Figure 1: Clinical outcomes after 24 months: adjusted ACRPedi30/50/70/90, inactive disease, CHAQ and JADAS-10 score, based on GEE analyses on imputated data


aACRpedi30
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Time (months)
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Time (months)
aACRpedi70
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Time (months)
aACRpedi90
%fulfilling ACRpedi90
Time (months)
CHAQ-score
Mean CHAQ-score
Time (months)
JADAS-10
Mean JADAS10
Time (months)
Inactive Disease
%fulfilling Inactive Disease
Time (months)
arm 1 Sequential monotherapy
arm 2 MTX + 6 wks prednisone
arm 3 MTX + Etanercept

O_13

Spinal radiographic progression in early axial SpA: 5-year data from the DESIR cohort

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Background

Spinal radiographic progression has been investigated in patients with r-axSpA, but not yet as thoroughly in early axSpA.

Objectives

To analyse the progression of spinal radiographic damage in patients with early axSpA.

Methods

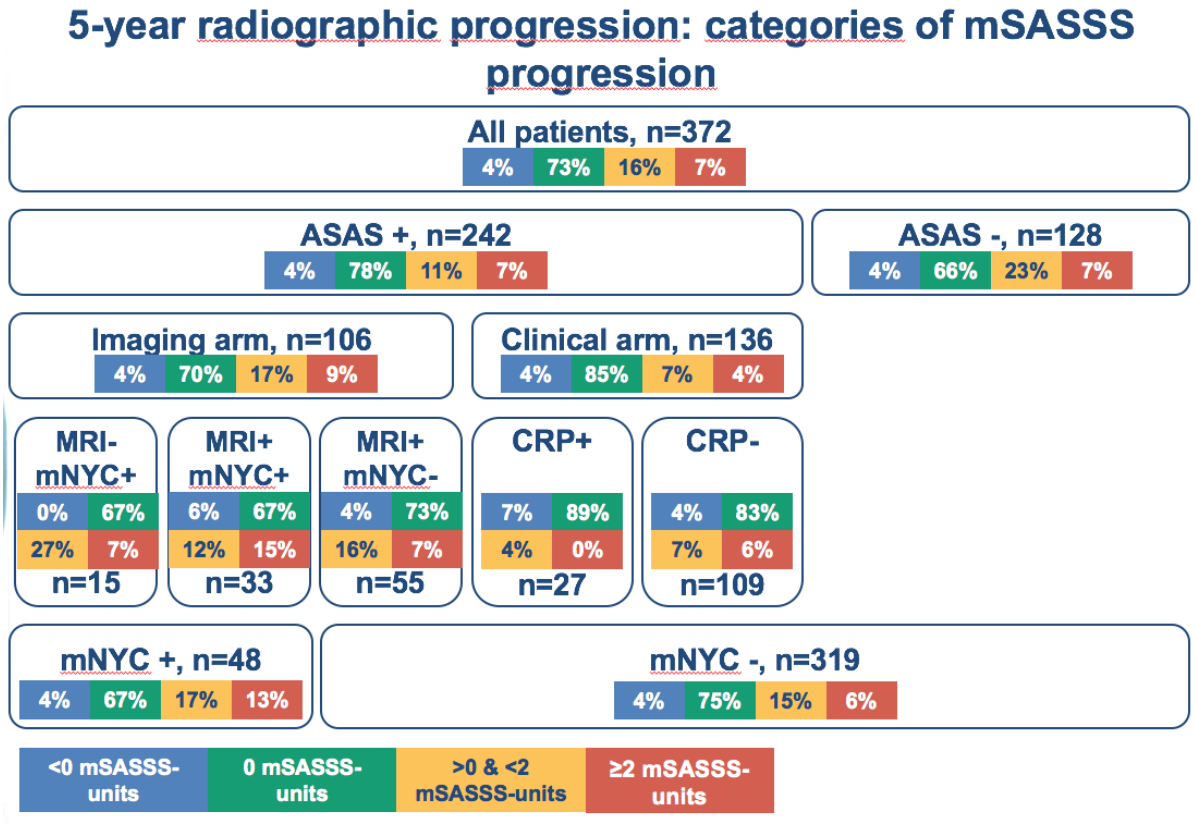
Five-year spinal radiographs from patients with early axSpA from the DESIR cohort were scored by 3 readers (average) according to the mSASSS (0-72). Change scores for all available intervals were calculated. The development of new syndesmophytes (2 out of 3 readers) was calculated as a net change: number of patients with positive change minus number of patients with negative change divided by total number of patients. Two- and 5-year mSASSS progression and development of new syndesmophytes were assessed in subgroups defined at baseline according to the ASAS axSpA criteria and its arms, mNYC and also to the presence of syndesmophytes.

Results

In total, 549 patients (mean age 34 (SD 9) years, 46% males, 63% fulfilling ASAS axSpA criteria, baseline mSASSS 0.5(1.5)) were included. Thirty-eight patients (7%) showed syndesmophytes at baseline, 42% of which were ASAS axSpA criteria negative. Mean mSASSS progression was 0.2(0.9) at 2 years and 0.4(1.8) at 5 years. 18% of the patients fulfilling the ASAS axSpA criteria showed a 5-year positive mSASSS change (>0), compared to 30% in those not fulfilling the criteria (Figure). 26% of the patients fulfilling the imaging arm had a positive change: highest positive change in MRI-mNYC+ (34%), followed by MRI+mNYC+ (27%) and lastly MRI+mNYC- (23%). Mean mSASSS progression was highest in the mNYC+MRI+ group (1.3(4.0)). Eleven percent of the patients fulfilling only the clinical arm of the ASAS criteria had a positive change in mSASSS at 5 years, mean change of 0.1(0.7). Patients with baseline syndesmophytes (across all subgroups) had the highest progression: 2.7(5.0) mSASSS-units. At 5 years, 7% of all patients had a net change of any new syndesmophyte; this was 6% for ASAS+, 9% for ASAS-, 10% for the imaging arm (18% for mNYC+MRI+) and 3% for patients fulfilling the clinical arm only. Seventeen percent of the mNYC+ patients had a net change in new syndesmophytes as well as 42% of the patients with baseline syndesmophytes.

Conclusion

Spinal radiographic progression, though limited in early axSpA, can be captured already at 2 years of follow-up. Inflammation and damage in the SIJ are associated with a higher radiographic progression. The presence of baseline syndesmophytes strongly predicts the development of further structural damage already early in the disease.



O_14

Progression Of Structural Damage On MRI Of The Spine And Sacroiliac Joints In Patients With Axial Spondyloarthritis Is Limited: The 5 -Year Results In The DESIR Cohort

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[1]LUMC, Leiden, Netherlands, [2]ARC, Amsterdam, Netherlands, [3]Hospital Cochin, Paris,France

Background
Reliably detecting radiographic structural change in patients with axial spondyloarthritis (axSpA) is difficult. Magnetic resonance imaging (MRI) is an alternative for radiographs to assess structural damage. However, the utility of MRI capturing longitudinal structural changes has been poorly studied.
Objectives
To evaluate structural changes on MRI of the SIJ (MRI-SIJ) and spine (MRI-spine) in patients with early axSpA over a period of five years.
Methods
Patients with early (≤3 years) axSpA (DESIR cohort) were included. MRI-SIJ and MRI-spine were obtained at baseline and 5 years and scored by 3 central readers blinded for chronology. Sacroiliac and spinal structural damage (MRI-SIJ-STR resp. MRI-spine-STR) were defined according to 3 binary rules (A1: ≥ 3 fatty lesions; B1: ≥ 3 erosions; and C1: ≥ 5 fatty lesions and/or erosions) and 3 continuous scores (A2: number of fatty lesions; B2: number of erosions; and C2: number of fatty lesions/erosions. For binary outcomes, structural damage was defined by agreement of at least 2 out of 3 readers and the % of net-progression by subtracting the number of patients that 'improved' from those that 'worsened' divided by the total number of patients with complete baseline and 5-year data. For continuous outcomes, the mean of the 3 readers was used and the difference between year 5 and baseline was calculated.
Results
In total, 151 and 145 patients had complete MRI-SIJ and MRI-spine data available, respectively. The percentages of net-progression at SIJ-level are summarized (figure). These were 7.9%, 0.7% and 6.6% for the binary outcomes A1, B1 and C1 respectively. The percentage of 'improvement' (4.6%) was almost as high as the percentage of 'worsening' (5.3%) for definition B1 (≥3 erosions); while no 'improvements' were seen by the 3 readers for definition A1 (≥3 fatty lesions). Similar differences were seen for mean (standard deviation) change of the 3 MRI-SIJ-STR continuous outcomes (A2: 0.83 (2.20); B2: 0.20 (1.39); and C2: 1.02 (2.60); p<0.01 for all). Longitudinal MRI-spine-STR net change was almost absent (A1: 0.7%; B1: 0.0%; C1: -0.7%) considering the binary outcomes, and small considering definition A2 (0.14 (0.48); p<0.01) and C2 (0.18 (0.52); p<0.01) but absent for definition B2 (0.03 (0.24); p=0.109).
Conclusion
These results suggest that patients with early axSpA only show modest structural progression on MRI-SIJ and that fatty lesions are more sensitive to change compared to erosions. In this early axSpA population, MRI-detected structural progression in the spine is very limited.

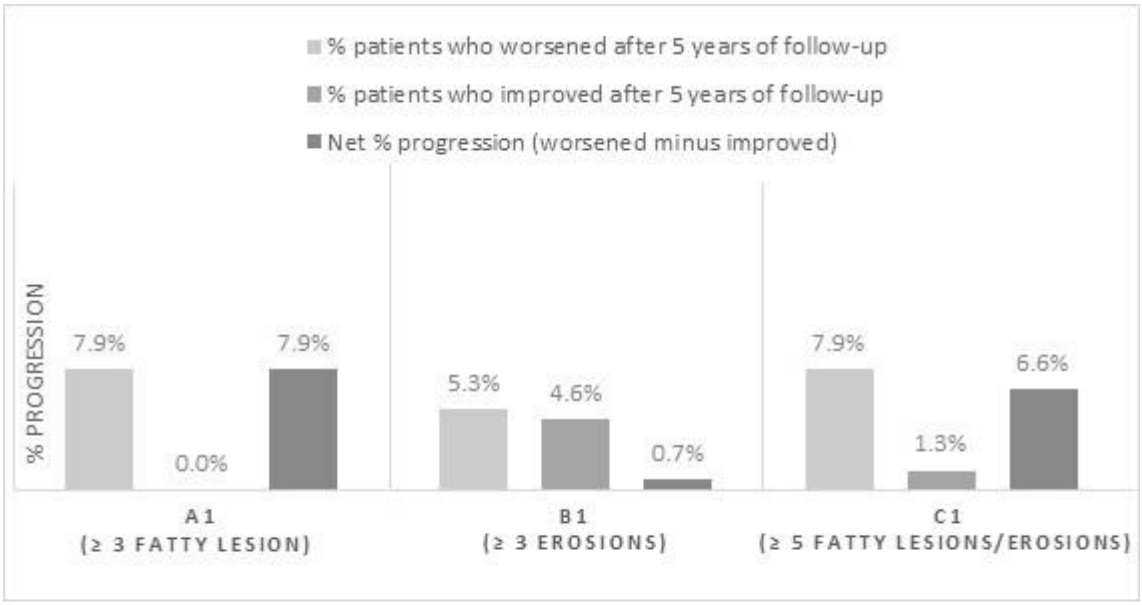

Figure. Changes in binary MRI-SIJ-STR outcomes assessed in the completers population (N=151). MRI-SIJ-STR, structural damage on magnetic resonance imaging of the sacroiliac joints.

O_15

The prevalence of radiographic entheseal anomalies at the hip and pelvic region in patients with ankylosing spondylitis

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Introduction

Enthesitis is one of the features of ankylosing spondylitis (AS). High prevalence of structural and inflammatory ultrasound lesions of peripheral entheses are found in AS patients[1]. There are also several entheseal sites at the pelvis and hip region but little is known about the presence of structural entheseal anomalies at these sites in AS. Therefore, our aim was to study the prevalence of radiographic entheseal anomalies at the hip and pelvic region in patients AS.

Methods

The present analysis was performed in 214 patients from the Groningen Leeuwarden Axial SpA (GLAS) cohort study, who were included between november 2004 and december 2010 and had available anteroposterior (AP) pelvis radiographs at baseline least 4 years of follow up. All patients fulfilled the modified New York criteria. The baseline radiographs were scored by two trained readers blinded for patient characteristics and treatment. Anomalies with absolute agreement were reported. The entheseal sites scored were: trochanter major, trochanter minor, os ischium, crista iliaca, both left and right side and symphysis pubis. The following 3 anomalies were scored: cortical irregularities/erosions, calcifications and enthesophytes.

Results

Of the 214 patients, 148 (69%) were male, mean age was 42.5 ± 11.6, (80%) was HLAB27 positive and median symptom duration was 16 years (8-24). Reader agreement on the entheseal anomalies was moderate to excellent with Cohen's kappa's between 0.474 and 0.882. 122 patients (51%) showed entheseal anomalies with 309 lesions in total. The most prevalent lesions were irregularities/erosions 220 (71%), followed by enthesophytes 71 (23%) and calcifications 16 (5%). Most lesions were found at the os ischii 168 (54%), followed by the tuberculum majus 42 (14%), crista iliaca 40 (13%), tuberculum minus 30(10%) and symphysis pubis 29 (9%).

Conclusion

In this AS cohort a high prevalence of radiographic entheseal anomalies at the hip and pelvic region was found. Irregularities and erosions were most frequently found, especially at os ischii. These new findings concerning structural entheseal anomalies at the pelvis and hip region contributes to the knowledge of entheseal involvement in AS.

Table 1: Prevalence of radiographic entheseal abnormalities at the hip and pelvic region in patients with AS

Table 1. Prevalence of radiographic entheseal abnormalities at the hip and pelvic region in patients with AS

	all entheseal abnormalities		Erosion/irregular		Calcification		Enthesophyte	
	Patients	Lesions	Patients	Lesions	Patients	Lesions	Patients	Lesions
All entheseal sites	122	309	119	220	11	16	48	71
Tuberculum majus	31	42	11	16	11	12	9	12
Tuberculum minus	26	30	10	12	0	0	16	18
Os ischii	90	168	75	147	4	4	11	17
Crista iliaca	30	40	16	20	0	0	14	20
Symphysis pubis	29	29	25	25	0	0	4	4

O_16

Which scoring method depicts spinal radiographic damage in (early) axial spondyloarthritis best? Five-year results from the DESIR cohort

M.S. Ramiro[1], P. Claudepierre[2], A. Sepriano[3], M. van Lunteren[3], A. Molto[4], A. Feydy[4], M.A. D'Agostino[5], D. Loeuille[6], M. Dougados[4], M. Reijnierse[3], D. van der Heijde[3]

[1]Zuyderland Medisch Centrum, Heerlen, Netherlands, [2]Université Paris Est Créteil, CréTeil, France, [3]LUMC, Leiden,Netherlands, [4]Paris Descartes University, Paris, Netherlands, [5]Université Versailles-Saint Quentin en Yvelines Boulogne-Billancourt, Paris, [6]University of Nancy, Nancy, France

Background

Scores capturing spinal radiographic damage have been proposed and compared in r-axSpA. In early phases of the disease, it is still unknown how these perform.

Objectives

To compare the performance of different spinal radiographic damage scoring methods in patients with early axSpA.

Methods

Five-year spinal radiographs from the DESIR cohort were scored by 3 readers (averaged) for the calculation of different radiographic methods (Table). Following the OMERACT filter, scores were compared with regard to truth, discrimination (sensitivity to change and reliability) and feasibility. Baseline status scores, and 2- and 5-year change scores were calculated for each of the methods, as well as the proportion of patients with a net change (number of patients with a positive change minus number of patients with a negative change divided by all patients) above the smallest detectable change (SDC). The proportion of total variance explained by the patient ('true variance') was calculated for the change scores, as a measure of reliability, using ANOVA.

Results

In total, 699 patients (mean age 34 (SD 9) years, 47% males) had at least one radiograph available. Mean baseline and 5-year change scores were: SASSS 0.2(0. 7) and 0.4(1.3), mSASSS 0.4(1.5) and 0.5(2.0), RASSS 0.5(1.7) and 0.7(2.5), BASRI-spine 1.0(1.2) and 0.3(0.6), BASRI-spine-thoracic: 1.1(1.4) and 0.3(0.7), BASRI-total 1.0(1.3) and 0.3(0.6) and BASRI-total-thoracic 1.2(1.4) and 0.4(0.7), respectively. SDCs and proportion of 2- and 5-year change, including net change, are presented in the Table. The mSASSS and the RASSS performed the best in terms of capturing the signal (positive change) despite the noise (negative change).

The proportion of variance explained by the patient was highest for the mSASSS and RASSS (85% for both 5-year progression scores vs 50-55% for other methods). The proportion of patient variance in the thoracic segment of the RASSS was unsatisfactory (46% for progression).

In what concerns feasibility, all scores seemed feasible, but the thoracic segment was missing in up to 7% of the cases, thus not allowing computation of BASRI modifications to include that segment.

Conclusions

The existing scoring methods to assess spinal radiographic damage performed well in early phases of axSpA. The mSASSS and RASSS captured most change. There was no clear gain in additionally scoring the thoracic spine for the RASSS while an increased noise was introduced. The mSASSS remains the most sensitive and valid scoring method in axSpA, including early phases of the disease.

Table: Two- and 5-year change, above the smallest detectable change, across the different radiographic scoring methods

	2-year Change > SDC (N = 357)				5-year Change > SDC (N = 265)			
	SDC	Positive change N (%)	Negative change N (%)	Net change N (%)	SDC	Positive change N (%)	Negative change N (%)	Net change N (%)
SASSS (0-72)	0.75	11 (3)	0 (0)	11 (3)	1.17	30 (11)	0 (0)	30 (11)
mSASSS (0-72)	0.88	22 (6)	2 (0.6)	20 (6)	1.10	34 (13)	1 (0.4)	33 (12)
RASSS (0-84)	1.00	17 (5)	0 (0)	17 (5)	1.19	44 (17)	0 (0)	44 (17)
BASRI-spine (0-12)	0.59	30 (8)	14 (4)	16 (4)	0.74	32 (12)	1 (0.4)	31 (12)
BASRI-spine-thoracic (0-16)	0.59	35 (10)	16 (4)	19 (5)	0.89	31 (12)	2 (1)	29 (11)
BASRI-total (0-16)	0.61	31 (9)	14 (4)	17 (5)	0.75	33 (12)	1 (0.4)	32(12)
BASRI-total-thoracic (0-20)	0.72	19 (5)	4 (1)	15 (4)	0.91	32 (12)	2 (1)	30 (11)

SDC: smallest detectable change; mSASSS: modified Stoke in Ankylosing Spondylitis Spine Score; RASSS: Radiographic Ankylosing Spondylitis Spinal Score; SASSS: Stoke Ankylosing Spondylitis Spine Score; BASRI: Bath Ankylosing Spondylitis Radiology Index

O_17

High prevalence of axial spondyloarthritis in patients with acute anterior uveitis and chronic back pain - preliminary results of the Sp-EYE study

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Background
Acute anterior uveitis (AAU) can be associated with axial spondyloarthritis (axSpA). Previous studies even described undetected axSpA in 40% of the patients with noninfectious AAU. Currently, axSpA patients still suffer an important diagnostic delay.
Objective
To investigate whether referral of all patients with AAU and chronic back pain results in a high prevalence of newly diagnosed axSpA patients.
Methods
In April 2017 a prospective (ongoing) observational study was started to include all patients with noninfectious AAU and back pain (≥3 months, started < age of 45 years) who were referred from nine Ophthalmology clinics to the Rheumatology department of the VU university medical center. Exclusion criteria were: history of a rheumatic or other known systemic disease associated with uveitis. At the Rheumatology department sociodemographic, clinical (e.g. duration of back pain, extra-articular manifestations, BASMI), laboratory (HLA-B27, C-reactive protein) and radiographic parameters were collected, as well as patient reported outcome parameters (e.g. BASDAI, ASDAS, ASAS Health Index). The diagnosis of axSpA was made by the rheumatologist. According to the ASAS criteria, diagnosed patients were classified into radiographic or non-radiographic axial spondyloarthritis.
Results
In the first year, 42 patients were referred to the Rheumatology department, of whom 32 (age 35 years; 47% female) met all the inclusion criteria. At referral, 63% of the patients already had a history of more than one AAU and the median back pain duration was 11 years (table 1). AxSpA was diagnosed in 10 patients (31%, all HLA-B27 positive), of whom four fulfilled the criteria for radiographic and six for non-radiographic axSpA. Another 11 patients (34%, six HLA-B27 positive) were considered to be suspicious for early axSpA. An ASDAS-CRP score corresponding to a high disease activity (ASDAS ≥2.1) was found in 57% of the patients with a new diagnosis or a suspicion for axSpA. Treatment was started in 20 patients, mostly with nonsteroidal anti-inflammatory drugs (in 18). In one patient a tumor necrosis factor alpha inhibitor was started shortly after diagnosis, because of the severity of the axSpA.
Conclusion
In this study the referral of noninfectious AAU patients with chronic back pain led to a notably high number of new diagnoses of axSpA (31%). Another third of the patients was considered to be suspicious for beginning axSpA, requiring further follow up. These results stress the importance of systematic referral of AAU patients from the ophthalmologist to the rheumatologist in order to improve early recognition of axSpA.

Table 1. Patient and disease characteristics at referral

Table 1. Patient and disease characteristics at referral.

	Overall (N=32)		Definite AxSpA (N=10)		Suspicion of early axSpA (N=11)		No suspicion of axSpA (N=11)	
Age (years)	35	(29-48)	35	(30-53)	31	(27-42)	41	(34-54)
Gender – male (%)	17	(53)	8		5		4	
Back pain								
Age start back pain	24	(17-34)	29	(22-36)	20	(16-27)	24	(15-36)
Years since onset back pain	11	(5-23)	8	(4-19)	12	(2.8-21)	15	(5-24)
Currently back pain (%)	28	(88)	9		10		9	
Inflammatory back pain (clinically)	9	(28)	7		2		0	
Inflammatory back pain (ASAS)	20	(63)	9		8		3	
SpA characteristics								
Acute anterior uveitis	32	(100)						
Number of AAU	2	(1-4)	3	(2-10)	2	(1-3)	1	(1-3)
>1 AAU attacks at referral	20	(63)	8		7		5	
HLA-B27 positive (%)	20	(63)	10		6		4	
SpA features (ASAS) – amount	3	(±1)	4.5	(4-5)	3	(2-4)	2	(1-3)
Sacroiliitis - mNY criteria	4	(13)	4		0		0	
Disease activity								
C-reactive protein >7 mg/L	6	(19)	4		0		2	
BASMI score	1.7	(1.2-2.7)	3	(2-5.2)	1.4	(1.2-2.0)	1.4	(0.6-2.0)
Back pain, NRS	4	(1-6)	2	(2-6)	5	(3-6)	4	(1-6)
Patient global disease activity, NRS	5	(2-7)	5	(2-6)	7	(2-7)	5	(2-6)
BASDAI	3.0	(2-5)	2.2	(1.6-4.2)	4.0	(2.8-6.3)	3	(2-4)
ASDAS-CRP	2.2	(1.8-2.7)	2.0	(1.6-4.2)	2.3	(2.0-2.8)	2.0	(1.1-2.8)
ASDAS-CRP ≥2.1	16	(50)	4		8		4	
ASAS Health Index	4	(2.5-6)	3	(2-4)	6	(3.5-9)	5	(1-6)
Treatment started								
NSAID*	18	(56)	10		5			
DMARD **	1	(3)	0		1			
TNF inhibitor	1	(3)	1		0			

All values are reported as numbers (percentage), mean (±standard deviation) or median (with 1st and 3d quartile). *Two patients (both diagnosed with axSpA) already chronically used a nonsteroidal anti-inflammatory drug. **In one patient methotrexate was started because of persistent anterior uveitis and enthesitis.

AxSpA, axial spondyloarthritis; AAU, acute anterior uveitis; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score – C-reactive Protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Score; BASMI, Bath AS Metrology Index; DMARD, disease modifying antirheumatic drug; mNY, modified New York criteria for sacroiliitis; nrs, numerical rating score (0-10); NSAID, nonsteroidal anti-inflammatory drug; SpA, spondyloarthritis; TNF, tumor necrosis factor.

O_18

Sick leave and its predictors in ankylosing spondylitis: long-term results from the Outcome in Ankylosing Spondylitis International Study

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Background

Sick leave (SL) among patients with ankylosing spondylitis (AS) is a relevant outcome for individuals and society. Disease-related factors, contextual factors, but also SL itself may be risk factors for future adverse work outcome.

Objective

To investigate the occurrence of AS-related SL over 12 years and to explore which factors predict SL.

Methods

Data from employed patients from the Outcome in Ankylosing Spondylitis International Study were used. At each visit, patients indicated the occurrence of SL (yes/no) in the previous inter-assessment period. Cox regressions were used to predict the hazard for a first episode of SL. Generalized estimated equations (GEE) were used to investigate the association between SL and (time-lagged) predictors. To investigate whether SL predicts new SL, SL in the first year was included as covariate in a separate GEE analysis. Separate multivariable models for ASDAS, BASDAI and BASFI were computed.

Results

139 patients (76% males, mean (SD) age 38.7 (10.0) years) were at risk for SL for an average period of 7.9 years, of whom 88 (63%) reported any SL. In both the Cox baseline predictors analyses (HR [95%CI]) and the time-varying GEE analyses (OR [95%CI]), ASDAS (1.67 (1.23-2.28)[HR]; 1.48 (1.07-2.03)[OR]); BASDAI (1.33 (1.18-1.51)[HR]; 1.31 (1.15-1.49)[OR]) and BASFI (1.17 (1.02-1.34)[HR]; 1.31 (1.16-1.47)[OR]) were associated with SL in separate models, but only in patients with a low educational level. Further adjustment for job type did not lead to different results. SL during the first year predicted SL over time (OR: 2.62-8.37 in different models, all $p<0.05$), independently of educational level, disease activity or physical function.

Conclusion

Disease activity and physical function predict SL, but only in patients with a low educational level. Prior SL results in future SL, and SL should be considered a signal for support to prevent future adverse work outcome. Research into which SL is beneficial with regard to recovery and which SL is a risk for work disability is needed.

O_19

mTOR blockade by rapamycin decreases arthritis and spondylitis development and severity in HLA-B27 transgenic rats

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Background
HLA-B27 misfolding is thought to play an important role in the pathogenesis of spondyloarthritis (SpA), possibly through triggering of ER stress and the unfolded protein response. One of the mechanisms that regulates the unfolded protein response is autophagy. Autophagy is a process that degrades proteins, cytoplasmic particles and organelles in lysosomes and is regulated by protein kinases, mechanistic target of rapamycin (mTOR) and AMP activated protein kinase.
Objective
To study whether blockade of mTOR will affect spondyloarthritis development and/or severity in the *Mycobacterium tuberculosis* (*M. tub*) induced disease HLA-B27 tg rat model.
Methods
6 weeks old, female or orchiectomized male HLA-B27/Huβ2m transgenic rats were immunized with 60-90 µg heat-inactivated *M. tub* in IFA. Rats were prophylactically or therapeutically treated three times a week intra-peritoneally with 1.5 mg/kg rapamycin or vehicle. Clinical measurements included weight, clinical scores for spondylitis and arthritis, and hind paw swelling measured by plethysmometry. After 5 weeks of treatment rats were sacrificed; axial and peripheral joints were isolated for histology and metacarpophalangeal joints, spleen and lymph nodes were isolated for RNA isolation.
Results. In the prophylactic experiment 72.7% (8/11) and 18.2% (2/11) rapamycin treated rats developed arthritis and spondylitis compared to respectively 100% (13/13; p=0.0225) and 92.3% (12/13; p<0.0001) control animals. Also severity of arthritis and spondylitis was significantly decreased in rapamycin treated animals compared to control treated animals; mean arthritis severity of diseased rats was respectively 0.45 versus 7.15 on a scale from 0-12 (p<0.0001) and mean spondylitis severity was respectively 0.18 versus 2.07 on a scale from 0-3 (p<0.0001). Clinical findings were confirmed by histology with a significant decrease of inflammation (p<0.0001), bone- and cartilage destruction (p=0.0021) and new bone formation (p=0.0010) in peripheral joints of rapamycin treated rats compared to vehicle treated rats and a similar trend was observed in spinal joints. Also in a therapeutic setting rapamycin treatment decreased arthritis severity (mean score of 6 compared to 8.8 in controls; p=0.0317) and spondylitis severity (mean score of 1.23 compared to 2.8 in controls; p=0.0159). Histology for the therapeutic experiment is currently being performed as well as RNA analyses for autophagy genes and pro-inflammatory cytokines, like IL-17A and TNF.
Conclusion
mTOR blockade significantly suppressed arthritis and spondylitis in the *M. tub* induced disease HLA-B27 transgenic rat model of SpA.

O_20

The Rheumatoid Factor response is composed of multiple reactivities against different epitopes

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Background
Rheumatoid arthritis (RA) is a complex autoimmune disorder in which autoantibodies likely play an important role. Rheumatoid factors are autoantibodies that bind to the constant domain (Fc) of immunoglobulin G (IgG). It is known that they can bind in various ways; most RA patients probably have multiple types of rheumatoid factors that all bind different parts of antibodies. It is presently unknown how this differs between patients. Furthermore, it is possible that RF responses in RA have a different reactivity pattern compared to those present in other diseases and in RF+ healthy donors. Currently, RA-specific rheumatoid factors have not been identified.

Objectives
Develop a method to identify and dissect different RF responses. Classify the RF response in different stages of RA. Characterize differences in reactivity between RF responses in the context of RA and RF responses in other diseases or healthy donors.

Methods
Variants of human IgG antibodies to which only a few different types of rheumatoid factors can bind at a time were generated and used as target antibodies in newly developed ELISA-based RF assays. RF responses were analyzed in healthy donors, arthralgia patients and RA patients at different disease stages.

Results
RF responses in all cohorts were shown to be primarily directed against epitopes at the interface of the second and third IgG heavy chain domains (CH2-CH3) and the tip of the CH3 domain. The generated target antibodies were able to separate these RF responses and discriminate them from RF responses targeting epitopes outside these reactivity hotspots. Furthermore, certain RF responses against the CH2-CH3 interface were shown to be dependent on the presence of a single specific amino acid residue.

Pilot experiments using the target antibodies in clinical cohorts revealed that, in arthralgia patients and RA patients at various disease stages, the pattern of RF reactivity differs from patient to patient and between cohorts. The degree to which an RF response against the CH2-CH3 interface depends on the single specific amino acid residue varied substantially between patients. One particular RF response pattern, with RFs binding only the CH3 domain, was found exclusively in non-RA patients and healthy donors.

Conclusions
Using newly developed target IgGs, RF responses against different epitopes can be characterized. RF response patterns differ between RA and non-RA cohorts and between RA patients. These new tools may lead to identification of RA-specific RF responses and provide more insight into the pathogenic role of these autoantibodies.

O_21

The omega-6 fatty acid adrenic acid is a novel pro-resolving mediator potently reducing joint swelling in a mouse arthritis model

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Background
Oxidative derivatives of poly unsaturated fatty acids play a prominent role in inflammation and its resolution. During self-resolving inflammation, a temporal switch takes place from pro-inflammatory lipid mediator production during initiation of inflammation towards anti-inflammatory and pro-resolving lipid mediators during the resolution phase. It is generally believed that omega-6 fatty acids derivatives, such as the arachidonic acid (AA) derived lipid mediators prostaglandin E2 (PGE2) and leukotriene B4 (LTB4), are pro-inflammatory. In contrast, omega-3 derivatives are usually anti-inflammatory and pro-resolving. These include several lipid mediator families, such as maresins, protectins and resolvins derived from omega-3 fatty acids EPA and DHA. In this study, we identify potent anti-inflammatory effects and pro-resolving properties of an omega-6 fatty acid, adrenic acid (AdA) and study its effect on inflammatory arthritis.
Methods
AdA was measured in peritoneal exudates obtained during the zymosan-induced murine peritonitis model. Pro-resolving function of AdA was evaluated *in vitro* in human peripheral blood neutrophils, THP-1 cells and GM-CSF polarized macrophages differentiated from peripheral blood monocytes. Incorporation of AdA in higher order cellular lipids was assessed using LC-MS. The in vivo effects of AdA were investigated in the K/BxN serum transfer model of arthritis upon treatment with 2,5 mg/mouse/day AdA starting with day -3 until the end of the experiment.
Results
AdA accumulated during the resolution phase of inflammation in the zymosan-induced peritonitis *in vivo*, indicating its pro-resolving function. Specifically in human neutrophils , but not macrophages, AdA inhibited the LTB4 production pathway by blocking AA release. As a consequence, AdA inhibited further recruitment of neutrophils in a migration assay in vitro. In THP-1-derived and GM-CSF polarized monocyte-derived macrophages, AdA enhanced phagocytosis of zymosan particles. AdA was taken up by neutrophils, but did not affect the activity of lipases known to be involved in AA release from phospholipids or triglycerides. Rather, AdA induced rapid (re-) incorporation of AA into both triglycerides and phospholipids, suggesting that AdA could act on enzymes facilitating this process. *In vivo*, AdA promoted resolution of joint inflammation in the K/BxN serum-transfer model of arthritis.
Conclusions
Our findings indicate that AdA has potent pro-resolving functions, both in vitro and in an arthritis model in vivo, thereby revealing a novel omega-6-derived lipid mediator involved in resolution of inflammation.

O_22

Salivary Gland Stem Cells Age Prematurely in Primary Sjögren's Syndrome

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Background

Hyposalivation is frequently observed in primary Sjögren's syndrome (pSS). This dysfunction is not correlated with lymphocytic infiltration commonly associated with pSS, as frequently presumed. Salivary gland SG homeostasis is controlled by salivary gland stem cells (SGSCs), which differentiate and proliferate into saliva-producing acinar cells.

Objective

Given the non-functional nature of SGs in pSS, we sought to investigate the regenerative capacity of SGSCs in pSS and probe reasons behind the persistent state of hyposalivation.

Methods

SGSCs were isolated from SG biopsies of healthy control (HC), incomplete and complete pSS patients according to ACR-EULAR criteria and exposed to a self-renewal assay to assess proliferation ability. Mature organoid formation assays were performed to ascertain differentiation potential. Extracted DNA from SGSCs was analyzed for telomere length using STELA. To assess the effect of an inflammatory environment on SGSCs, self-renewal assays were performed with added IFNα, TNFα and IL-6. Immunostaining for p16 (senescence marker) and CD24 (stem cell marker) was performed on SG tissue. CD24 expression and cell cycle were analyzed in SGSC cultures by flow cytometry.

Results

SGSC yield from pSS biopsies was five-fold lower than from HC biopsies. pSS-SGSCs were capable of significantly lower degrees of proliferation, a classical characteristic of stem cells, when subjected to our self-renewal assay. Single cell-derived mature organoids containing amylase expressing acinar cells could be generated from HC-SGSCs, but not from pSS-SGSCs (Fig. 1a-c). Telomeres in pSS-SGSCs were significantly shorter than HC-SGSCs, suggesting senescence. Exposure of SGSCs to a IFNα, TNFα and IL-6 cytokine cocktail resulted in increased organoid forming efficiency. SGSC cultures contain a mixture of basal striated duct (BSD) and intercalated duct (ID) cells. Proinflammatory cytokine exposure decreased BSD cell number and increased in ID cell number, and expression of senescence-associated genes. $p16^{+}$ cells, indicative of senescence, were found localized to ID ducts in pSS tissue sections.

Conclusion

We suggest for the first time that hyposalivation in pSS is not *per se* caused by lymphocytic infiltration of the salivary glands only, but by exposure of SGSCs to pro-inflammatory cytokines leading to eventual SGSC senescence. These data open the door for new therapeutic interventions for hyposalivation in pSS such as generation of new SGSCs using iPS technology, and a deeper comprehension of pSS as a disease.

Caption 1: Salivary gland stem cells isolated from pSS biposies have severely limited differentiation potential.

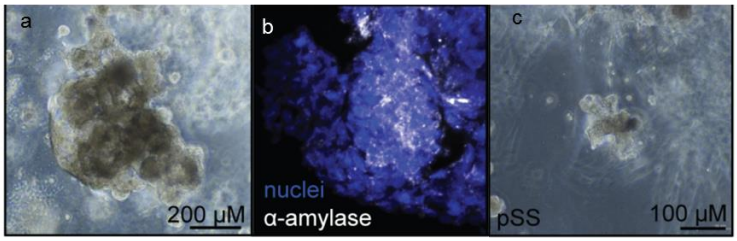

Figure 1. a) Mini salivary gland formation from healthy control SGSCs. B) α-amylase expression in differentiated mini glands, indicative of functional acinar cells. c) Attempted mini gland formation from pSS-SGSCs.

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O_23

Dysregulation of NF-?B in glandular epithelial cells results in Sjögren's-like features

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Objective

Hyposalivation and lymphocytic infiltration in salivary glands are common manifestations of primary Sjögren's syndrome. NF-kappa B (NF- κB) signaling is one of the most important proinflammatory pathways, and is inhibited by A20 (also known as TNFAIP3). Although mounting studies are pointing to the central role of epithelial cells in initiation of pSS, what exact function they perform the early stages remains poorly understood. In the current study we employ a mouse model using cytokeratin 14 (CK14) promoter-driven knockout of the NF- κB inhibitor A20 gene, to promote an inflammatory environment by epithelial cells and investigate this.

Methods

To generate knockout mice F2 generations of A20FL/FL mice (provided by Dr. Geert van Loo, Ghent University, Belgium) crossed with CK14Cre/WT mice were used. A20 gene expression was knocked out in KRT14+ cells, namely ductal and myoepithelial cells. Whole pilocarpine stimulated saliva was collected from A20-/- mice and wildtype (WT) littermate controls at 10, 20 and 30 weeks of age. Submandibular SGs were harvested at all time points for histological examination and qPCR.

Results:

In submandibular SGs of A20-/- mice at 30 weeks of age, 10% of all cells were CD45+ leukocytes and 3% were CD3+ T cells, both significantly more than controls (Figure 1 A-I). B cell proportion increased over time in A20-/- mice, but was not significantly different to controls (Figure 1 J-M). CD45+ cells formed immune foci (>50 CD45+ cells together) localized to striated ducts, present at significantly greater frequencies than control mice. CD45+ cells, T cells and occasional B cells in A20-/- mice also invaded striated ducts. Expression of the pro-inflammatory cyto/chemokines IFNɣ, TNFα, IL-6, CXCL10 and CXCL13 was also significantly greater in A20-/- mice. Functionally, both volume and mucin 10 content of whole stimulated saliva from A20-/- mice was significantly reduced compared to controls.

Conclusions

We present a model for epithelial cell involvement in pSS SG pathology development. We confirm that saliva production defects, foci formation and striated duct invasion can be triggered solely by immune activated epithelial cells.

O_24

Targeting NF-κB signalling in B cells: a potential new treatment modality for ANCA-associated vasculitis

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Background
The pivotal role of B cells in the pathogenesis autoimmune diseases such as ANCA-associated vasculitis (AAV) is well-established and further substantiated by beneficial therapeutic effects of rituximab (anti-CD20 B cell targeted therapy). However, this results in prolonged B cell depletion while long-lived plasma cells are not targeted. Thus, there is a need for novel therapeutics targeting the B-cell lineage in AAV. NF-κB signalling pathways that act downstream of various B cell surface receptors, including the B cell antigen receptor, CD40, BAFFR and TLRs, are crucially involved in B cell responses and may be suitable as novel targets.

Objective
To identify whether inhibition of NF-κB signalling by novel pharmacological inhibitors is effective in targeting B cell responses in general and more specifically blocks (auto)antibody production and plasmablast differentiation in B cells from AAV patients.

Methods
PBMC and sorted B cells from AAV patients and healthy donors were cultured with T cell-dependent (anti-IgM+anti-CD40+IL-21) and T cell-independent (CpG+IL-2) stimuli. NF-κB signalling was targeted in these cultures by small molecule inhibitors of NF-κB inducing kinase (NIK, non-canonical NF-κB signalling) and Inhibitor of κB kinase β (IKKβ, canonical NF-κB signalling). Downstream NF-κB signalling and nuclear NF-κB translocation was determined by Western blot and confocal imaging. Effects on B cell proliferation and differentiation were determined by CFSE dilution assays and flow cytometric analysis of B cell markers. (Auto)antibody production was measured by ELISA.

Results
In B cells of AAV patients and healthy donors, targeting of NIK and IKKβ effectively inhibited downstream non-canonical or canonical NF-κB signalling, respectively. In a B cell stimulation assay, NIK and IKKβ inhibition significantly reduced T cell-dependent (anti-IgM+anti-CD40+IL-21) and T cell-independent (CpG+IL-2) B cell proliferation. In addition, B cell differentiation towards plasmablasts ($CD27^{++}/CD38^{+}$) and functional antibody production was attenuated by both NIK and IKKβ inhibitors. Interestingly, the effects of NIK inhibition appeared to be B cell-specific as T cell proliferation was largely unaffected.

Conclusion
These data demonstrate that inhibition of NF-κB signalling in AAV B cells results in the modulation of various B cell responses. Ongoing studies will indicate whether targeting of NF-κB signalling in B cells may be an effective novel treatment modality for AAV.

O_25

Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey

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Background

The EULAR and ACR recommendations regarding rheumatoid arthritis (RA) mainly focus on early phases of the disease and on pharmacological management. Nevertheless, some patients remain symptomatic despite treatment according to the current recommendations, which makes them difficult-to-treat.[1]The estimated prevalence of difficult-to-treat RA is around 5-20%. A difficult-to-treat RA classification needs to be defined to enable creation of recommendations on its comprehensive management.

Objectives

To compose a definition of difficult-to-treat RA and to explore items on its comprehensive management not covered by the current EULAR RA management recommendations.

Methods

An online survey was distributed among rheumatologists (in training). It consisted of 9 questions regarding the background of the respondents, aspects to be included in the definition of difficult-to-treat RA and missing items on its comprehensive management in the current EULAR management recommendations. Multiple-choice questions were used to assess the necessity of incorporating the following items into the definition: the disease activity level, e.g. the disease activity score assessing 28 joints (DAS28-ESR), presence of fatigue, number of disease-modifying anti-rheumatic drugs (DMARDs) that failed and the inability to reduce oral glucocorticoid (GC) treatment. Optional open questions were used to identify additional features for the definition of difficult-to-treat RA and to collect items on its comprehensive management not covered by the current EULAR recommendations.

Results

390 rheumatologists from 33 countries completed the survey between July and December 2017 (Figure 1a). 50% of the respondents would include signs suggestive of active disease or a DAS28-ESR score >3.2 in the definition (Figure 1b) and 41% fatigue. The most selected option for the number and category of DMARDs that had to have been used to be included in the definition was 1) Failure to ≥2conventional synthetic DMARDs and (Boolean) 2) ≥2biological or targeted synthetic DMARDs with different mechanisms of action (Figure 1c). 89% suggested including inability to taper oral GCs below 5 or 10mg. Over 400 responses to open questions were submitted, of which a selection is listed in Table 1.

Conclusion

This survey shows that difficult-to-treat RA is seen as a heterogeneous condition; next to signs of active disease, failure to DMARDs and inability to taper GCs may be included in the definition. The large number of respondents and of responses with regard to items not covered by the current EULAR RA management recommendations underscore the need for recommendations on comprehensive management of difficult-to-treat RA.

Figure 1. De Hair MJH et al.Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need.Rheumatology.2017;10.1093/rheumatology/kex349

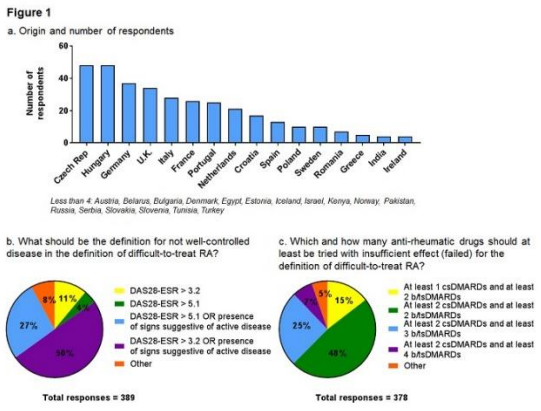

Table 1. Most frequent answers to the open questions

Please define any additional features and suggested criteria for difficult-to-treat RA	Please mention any clinically relevant situations which are not covered by the current EULAR RA recommendations
Time span with active disease despite treatment	Treatment adherence
Rapidly progressive erosions despite treatment	Persistent chronic pain without objective inflammatory signs
Adverse events to multiple agents	Coping problems
Comorbidities, e.g. fibromyalgia	Extra-articular manifestations

O_26

The use of MRI-detected synovitis to determine the number of involved joints for the 2010 ACR/EULAR classification criteria for Rheumatoid Arthritis - is it of additional benefit?

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Background
Because early classification is important in rheumatoid arthritis (RA), the 2010 criteria have been developed. These criteria suggest the use of imaging tools to ascertain synovitis. Although the development of the 2010-criteria was primarily data-driven, the suggestion to also use advanced imaging modalities to detect synovitis was included in the criteria based on expert opinion. The addition of advanced imaging modalities could substantially increase the number of involved joints and may improve the accuracy of the criteria. However, at present there is no evidence of the value of the addition of imaging.
Objective
We aimed to assess the value of MRI-detected synovitis to determine the number of involved joints on the performance of the 2010-ACR/EULAR classification criteria for RA.
Methods
277 patients with a clinical suspicion of RA consecutively included in the Leiden Early Arthritis Clinic (EAC)-cohort underwent 1.5T MRI of MCP-, wrist- and MTP-joints. Test characteristics of the 2010-criteria were calculated when the number of involved joints was determined with and without including MRI-detected synovitis. In addition we determined joint counts when other types of MRI-detected inflammation (bone marrow oedema (BMO), tenosynovitis or any inflammation) were regarded. Two outcomes were studied: disease modifying anti-rheumatic drug (DMARD)-initiation and 1987-criteria fulfilment during the first year.
Results
At baseline, 143 patients were classified as RA. When MRI-detected synovitis was considered, 14 patients additionally fulfilled the 2010-criteria. Of these, 64% (9/14) started DMARDs. When MRI-detected synovitis was also used to determine the number of involved joints the sensitivity (%, 95% CI) changed from 62 (55; 69) to 67 (60; 73), the specificity from 90 (82; 95) to 84 (73; 90) and the AUC from 0.76 to 0.75. The net reclassification index was -2.4%. The test characteristics and AUC of MRI-detected BMO and tenosynovitis were almost similar to that of MRI-detected synovitis. For the secondary outcome, fulfilment of the 1987-criteria, results were similar.
Conclusion
We found no scientific support that the use of MRI-detected synovitis is of additional benefit for the performance of the 2010 classification criteria.

O_27

Window or no window? Earlier is better when treating rheumatoid arthritis

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Background

Previous reports on a window of opportunity (WOO) in rheumatoid arthritis (RA) may be related to the use of slow acting csDMARDs. We investigated whether onset of action of therapy might influence whether there is a WOO or whether 'earlier is better'.

Objectives

To investigate the association between symptom duration at treatment onset and the achievement of sustained drug free remission (sDFR) in early RA-patients initiating therapy including fast acting prednisone or infliximab, compared to patients initiating csDMARD monotherapy.

Methods

We analysed the shape (non-linear or linear) of the association between symptom duration and achievement of sDFR (DAS<1.6 and no DMARDs for ≥1 year) in 3 cohorts: BeSt, IMPROVED and METEOR. Patients had arthritis symptoms <2 years. In BeSt, RA-patients (1987 criteria) were randomised to 4 targeted treatment strategies aimed at DAS≤2.4: arm 1 and 2 initiated csDMARD monotherapy, arm 3 csDMARDs and tapered high dose prednisone and arm 4 csDMARD and infliximab. In IMPROVED RA-patients (2010 criteria) were treated with csDMARD and tapered high dose prednisone. Subsequent treatment adjustments aimed at DFR. METEOR is an international observational cohort including daily practice data from RA-patients with a diagnosis and treatment according to the rheumatologist. We selected patients who initiated csDMARD monotherapy or a combination of csDMARD with prednisone or anti-TNF and at least 1.5 year follow-up.

We performed Cox regression with as outcome sDFR and as predictor symptom duration and used likelihood ratio tests to compare the fit of a linear model and a model with inclusion of natural cubic spline functions (resulting in a hyperbola).

Results

In BeSt (n=469), IMPROVED (n=421) and METEOR (n=1268) 54, 110 and 10 patients who initiated fast acting combination therapy, and 53 in BeSt and 15 in METEOR who initiated csDMARD monotherapy achieved sDFR. A non-linear model did not show a better fit for the data than a linear model (table 1). Thus, we did not find a curved relationship between time of treatment initiation and achieving sDFR. The best fit models indicate that the earlier treatment is started, the higher the likelihood of achieving sDFR (figure 1).

Conclusions

Our data suggest that there is no evidence for a WOO in early RA in 3 cohorts. This was not related to use of fast acting combination therapy instead of slow acting monotherapy nor was it dependent on strict treat-to-target in clinical trials. Instead, our data reaffirm that earlier is better when treating RA.

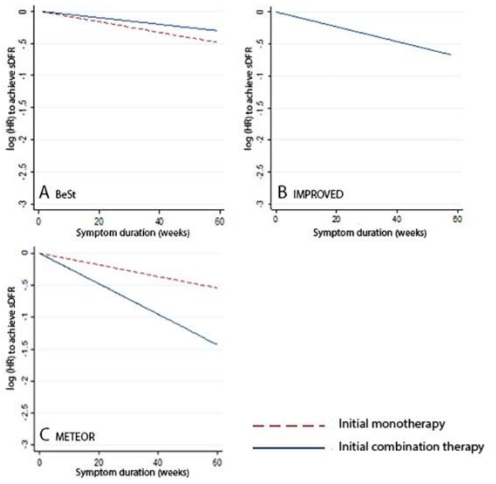

Figure 1. Best fit models to depict the relationship between symptom duration and sDFR in the BeSt (a) and IMPROVED (b) trial and in the METEOR registry (c). Applying natural cubic spline functions (allowing a curved relationship) did not result in a superior fit compared to a linear model.

Table 1. P-values of the likelihood ratio tests to compare the fit of a linear and a non-linear Cox regression model

	BeSt	IMPROVED[a]	METEOR
csDMARD monotherapy	0.609	--	0.678
Fast acting combination therapy[b]	0.743	0.337	0.457

[a]No monotherapy in IMPROVED. [b]Including prednisone or infliximab.

O_28

Do age and education influence the Disease Activity Score? An explorative analysis in the Norwegian cohort study NOR-DMARD

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Introduction
While ageing influences auto-immune inflammation and the structure of the joints, knowledge about its influence on appraisal of disease outcomes is more limited.
Objective
To examine the effect of age and education on the components of the 28-joint Disease Activity Score (DAS28-ESR) in patients with rheumatoid arthritis (RA).
Methods
Baseline data of Disease Modifying Anti-Rheumatic Drug (DMARD)-naive patients with RA from the Norwegian Register of DMARDs (NOR-DMARD) were used. Linear regression models, adjusted for gender and education (low, intermediate and high level), were used to investigate the strength of the association between age (<45, 45-65 and >65 years) and each DAS28-component (Erythrocyte Sedimentation Rate (ESR), 28-tender joint count (28-TJC), 28-swollen joint count (28-SJC), and patient global assessment of disease activity (PGA)). Adjusted scores for components of DAS28 and total DAS28-ESR were computed and relative change across age categories was explored. Interactions between age and gender and age and education were also tested.
Results
Baseline data from 2037 patients (mean (SD) age 55.2 (14.0) years, 68% female) were available. Regression models were stratified for gender (p –interaction <0.05); education was a significant covariate in all regression analyses. Older males (>65 years) with an intermediate level of education would have a 21% higher ESR and 14% higher 28-SJC, as compared to their younger counterparts (<45 years). For females in the intermediate education category, the corresponding differences were 16% and 15%, respectively. Conversely, differences in 28-TJC and the PGA between the highest and lowest age group were negligible in both males and females (Table 1). In absolute effects on DAS28, this means that in male patients the adjusted DAS28 for those >65 years was 4.8 compared to 4.3 in patients <45 years (females 5.0 compared to 4.6). For low and high levels of education, the results were comparable in terms of relative contribution to each DAS28-component.
Conclusion
As expected, DAS28 increases with age. However, the components of DAS28 increase at different rates. The age-related increase in ESR and 28-SJC without a simultaneous increase in 28-TJC and PGA might imply that age-related processes (e.g. osteoarthritis and physiological increase in ESR) drive the DAS28 in older patients. The observed patterns were largely comparable between males and females. The age effect on DAS28 is relevant in a treat-to-target strategy and may be considered when identifying a defined target in individual patients.

Table 1. Effect of age on DAS28(ESR) for patients with an intermediate educational level.

Component Predicted values	< 45 years (reference) n = 181 (25%)	45 – 65 years n = 419 (58%)	> 65 years n = 123 (17%)	Difference between highest and lowest age group (%)
Males				
28-TJC	1.32	1.33	1.34	2%
28-SJC	0.62	0.66	0.71	14%[a]
PGA	0.57	0.59	0.58	2%
ESR	1.83	2.00	2.22	21%[a]
DAS28-ESR	4.34	4.58	4.83	11%
Females				
28-TJC	1.32	1.39	1.33	1%
28-SJC	0.59	0.63	0.68	15%[a]
PGA	0.67	0.68	0.68	1%
ESR	1.99	2.14	2.31	16%[a]
DAS28-ESR	4.57	4.84	5.00	9%

Abbreviations: TJC, tender joint count; SJC, swollen joint count; PGA, patient global assessment; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score.

[a]Difference in scores is significant (p < 0.05).

O_29

A combination of proteins as measured within the multi-biomarker disease activity score at presentation of RA identifies a group of ACPA-negative RA patients with high likelihood of developing DMARD-free sustained remission

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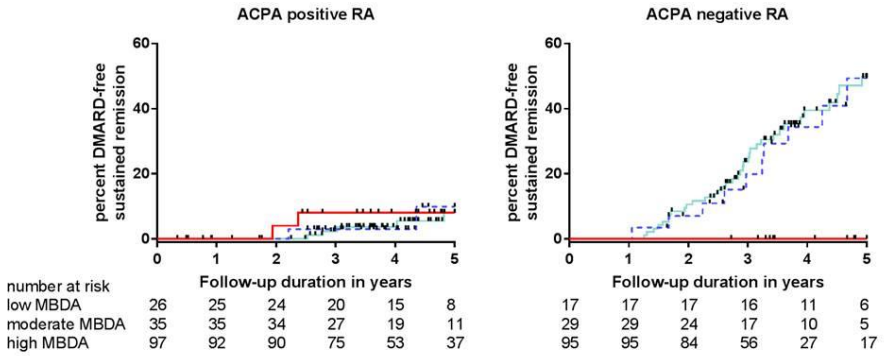
Background
Disease-modifying antirheumatic drug(DMARD)-free remission, the absence of synovitis after stopping DMARD-therapy, is increasingly being achieved by rheumatoid arthritis(RA) patients, but underlying mechanisms are unknown. The multi-biomarker disease activity (MBDA) score combines 12 serum biomarkers and is developed to measure RA disease activity. We hypothesized that the subgroup of RA patients that is most likely to achieve DMARD-free sustained remission is identifiable at disease presentation by cytokines such as those combined in the MBDA score.
Objective
To evaluate whether the MBDA score or its component cytokines at the presentation of RA are associated with ability to later achieve DMARD-free sustained remission.
Methods
299 RA patients were evaluated for the achievement of DMARD-free sustained remission during a median follow-up of 4.3 years. MBDA scores, with a scale from 1-100, were determined from serum concentrations of 12 biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, Leptin, Resistin, CRP, SAA) at disease onset, before DMARD treatment was started. Patients were categorized as having a low (<30), moderate (30-44) or high (>44) MBDA score. DMARD-free sustained remission was defined as the absence of synovitis (by physical examination) that sustained after discontinuation of all DMARD therapy (including biologics and systemic and intra-articular corticosteroids) for the entire follow-up period, but had to extend to at least one year after DMARD withdrawal. Analyses were stratified for ACPA.
Results
59 RA patients (20%) achieved DMARD-free sustained remission. In the total RA-group high MBDA scores were associated with achieving remission (high vs. low HR 3.79, 95%CI 1.18-12.22). Among ACPA-positive RA patients, MBDA scores were not associated with DMARD-free remission, whereas, among ACPA-negative RA patients, moderate or high MBDA scores associated strongly with achieving DMARD-free remission (moderate vs. low HR 9.40, 95%CI 1.21-72.85, high vs. low HR 9.73 95%CI 1.33-71.10, Figure). This association was independent of age and other clinical factors (moderate vs. low HR 6.96, 95%CI 0.88-55.31, high vs. low HR 8.19 95%CI 1.09-61.78). For ACPA-negative RA patients, the biomarkers C-reactive-protein, serum-amyloid-A and matrix-metalloproteinase-3 were individually associated with achieving DMARD-free sustained remission.
Conclusion
ACPA-negative RA patients who achieved DMARD-free sustained remission were characterized by moderate to high MBDA scores at disease presentation. This is the first evidence that a protein profile at disease onset can identify a subgroup of ACPA-negative RA patients with high likelihood of maintaining clinical remission after treatment withdrawal.

Caption 1: Kaplan-Meier plot showing achievement of DMARD-free sustained remission by category of MBDA score for ACPA-negative and ACPA-positive RA patients



O_30

Which cDMARD strategy is most effective in newly diagnosed seronegative rheumatoid arthritis patients;Post-hoc analysis of the tREACH study

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Background
Rheumatoid arthritis(RA) has a heterogeneous disease spectrum. Literature suggests that different disease subsets could be treated differently,with less aggressive treatment for seronegative-RA. Current treatment guidelines,however,do not take this into account, since evidence is lacking. Standardized treatment strategies in seronegative-RA are needed.
Objectives
To compare 1-year clinical efficacy of different initial treatment strategies in newly diagnosed,seronegative-RA patients according to 2010 classification criteria.
Methods
For this post-hoc analysis data of the stratified, single-blinded tREACH-trial were used. Eligible patients were stratified into 3 probability tertiles according to their likelihood of progressing to persistent arthritis based upon the Visser model. We selected all seronegative-RA patients from the intermediate and high stratum. Intermediate patients received one of the following initial treatment strategies:MTX 25mg/wk.(n=50),HCQ 400mg/day(n=40) or GCs orally starting with 15mg/day(n=41). High patients received triple DMARD combination therapy (MTX+SASP 2gr/day+HCQ+GCs(intramuscular/orally,n=17) or MTX+GCs orally(n=14).Treatment strategies were tightly controlled,with patients being examined every 3 months. Treatment decisions were based upon the original Disease Activity Score(DAS) threshold for low disease activity(DAS<2.4).Due to the poor comparability and low number of cases in the high stratum,primary outcomes were only analysed in the intermediate stratum. Primary outcomes were DAS and functional ability,measured with the Health Assessment Questionnaire(HAQ),over time,using a linear mixed model(LMM).In our final model we corrected for baseline DAS and HAQ.
Results
We included 162 seronegative-RA patients,of whom respectively 131(81%)and 31(19%) were in the intermediate and high stratum. Patients were mostly female(67%)with an average symptom duration of 161 days(95%CI:144-177). At baseline the average visser score was respectively 4 and 6 out of 13 for intermediate and high patients(Figure 1A). The difference in visser score was mainly due to the difference in erosions. Figure 1B-E show the DAS and HAQ over time per stratum and treatment. Our corrected LMM showed that there was no significant difference between treatment arms for DAS over time. After 3 months 33%,35% and 69% respectively treated with MTX,HCQ and GCs had an active disease(DAS ≥2.4),and needed treatment intensification(p<0.005 for HCQ and MTX versus GCs). After 1 year there was no difference between DAS over all treatment arms. Patients receiving HCQ showed a better functional ability over time compared to patients receiving other treatments(HCQ versus respectively MTX(β=-0.18,p.000)and GCs(β=-0.15,p.003)).
Conclusion
Seronegative-RA patients without erosions and a swollen joint count<10 can be treated with HCQ with similar efficacy to MTX. No conclusions can be drawn for seronegative RA patients who do not fulfill abovementioned criteria.

A Baseline characteristics and clinical response after 12 months for each induction therapy group, according to intention-to-treat

	Intermediate			High	
Characteristics	A.MTX (n=50)	B.HCQ (n=40)	C.GCs (n=41)	D. ITDT + GCs (n=17)	E.MTX + GCs (n=14)
Demographic					
Age (years), mean (SD)	57 (14)	54 (14)	53 (15)	56 (18)	59 (16)
Sex, female, n (%)	38(76)	24 (60)	27 (66)	12 (71)	7 (50)
Symptom duration (days), mean (SD)	155 (85)	177 (106)	152 (90)	180 (91)	137 (72)
Visser score, median (IQR)	4 (4-5)	4 (3-5)	4 (3-5)	6 (6-7)	6 (6-7)
Presence of erosion, n (%)	3 (6)	5 (13)	4 (10)	5 (35)	6 (43)
Das, mean (SD)	3.43 (0.92) (n=50)	2.93 (0.84) (n=39)	3.50 (0.93) (n=41)	4.02 (1.24) (n=17)	3.91 (1.26) (n=14)
HAQ, mean (SD)	1.20 (0.56) (n=42)	0.90 (0.61) (n=37)	1.03 (0.69) (n=36)	1.14 (0.58) (n=16)	1.48 (0.68) (n=14)
Response after 1 year					
Das, mean (SD)	1.71 (0.81) (n=41)	1.79 (0.96) (n=38)	1.66 (1.02) (n=28)	1.75 (0.77) (n=16)	1.94 (0.80) (n=13)
HAQ, mean (SD)	0.78 (0.55) (n=30)	0.77 (0.60) (n=24)	0.71 (0.68) (n=21)	0.87 (0.62) (n=14)	1.04 (0.68) (n=13)

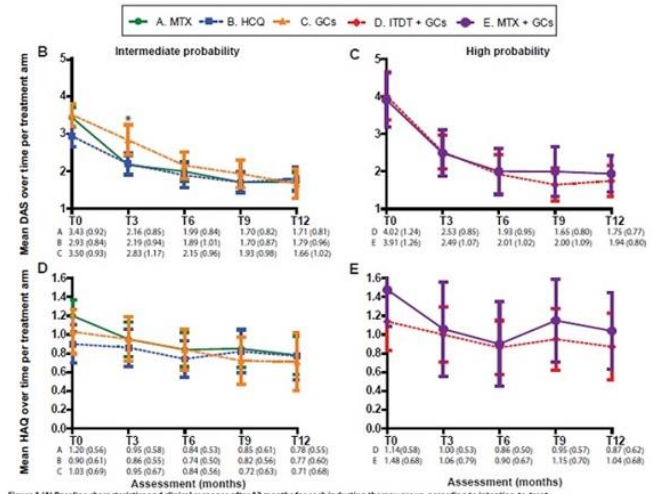

Figure 1 (A) Baseline characteristics and clinical response after 12 months for each induction therapy group, according to intention-to-treat. (B+C) Mean DAS over time per treatment arm. (D+E) Mean HAQ over time per treatment arm.
+ Not everyone filled out a (complete) questionnaire and therefore n is different for HAQ.
MTX 25 mg/wk, SASP 2 gr/day, HCQ 400 mg/day, GCs intramuscular or an oral tapering scheme starting with 15mg/day for treatment D and only oral for treatment C+E.
* GCs versus HCQ P.010 and MTX P.004.
Abbreviations: DAS, Disease Activity Score; GCs, glucocorticoids; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; iTDT, initial triple disease-modifying antirheumatic therapy; MTX, methotrexate; RA, rheumatoid arthritis; SASP, sulfasalazine.

O_31

Are ACPA associated with more bone loss over time in patients with rheumatoid arthritis?

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Background
Anti-citrullinated protein antibodies are one of the most important serological markers for rheumatoid arthritis and have been suggested to play a pathophysiologic role by directly binding to osteoclasts. However, the effect of anti-citrullinated protein antibodies on systemic bone mineral density and in particular their effect on changes in bone mineral density over time is currently unknown.
Objective
The aim of this study was to determine whether anti-citrullinated protein antibodies associate with changes in bone mineral density over time in patients with rheumatoid arthritis.
Methods
Yearly dual X-ray absorptiometry scores were performed during 5 years of follow-up in 412 patients with recent-onset rheumatoid arthritis participating in the IMPROVED study[1], a clinical trial in which patients were treated according to a remission- (disease activity score<1.6) steered strategy. The effect of the presence of ACPA on 1) Z-scores of lumbar spine and hip over time, and 2) prevalence of osteopenia/osteoporosis (defined as a T-score ≤-1) over time was analysed using generalized estimating equations. Analyses were adjusted for baseline age, gender, BMI and symptom duration and longitudinal smoking status, disease activity, prednisone intake, usage of bisphosphonates, calcium intake and serum 25-OH vitamin D levels.
Results
Anti-citrullinated protein antibody positive patients had a significantly lower lumbar spine (p=0.04) and hip (p=0.01) Z-score at baseline. There was no difference in prevalence of osteoporosis/osteopenia at baseline between anti-citrullinated protein antibody positive and anti-citrullinated protein antibody negative patients (OR (95% CI) 1.02 (0.55 to 1.19)). We hypothesised that serum positive patients would have more bone loss over time compared to serum negative patients. However, anti-citrullinated protein antibody positivity did not associate with a stronger decline in Z-score over time at lumbar (p=0.43) or femoral sites (p=0.67). Additionally, no effect of anti-citrullinated protein antibody positivity was found on the development of osteoporosis/osteopenia over time (p=0.23).
Conclusion
Anti-citrullinated protein antibody positive patients have a significantly lower baseline bone mineral density compared to anti-citrullinated protein antibody negative patients. Surprisingly, anti-citrullinated protein antibodies do not associate with a decrease in bone mineral density over time in patients who were treated according to a tight control strategy. These results indicate that anti-citrullinated protein antibodies alone do not contribute to bone loss after disease onset in the absence of inflammation/disease activity.

O_32

Familial Paget's disease of bone: Long-term follow-up of index families in The Netherlands

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Background
The aetiology of Paget's disease of bone (PDB) is still unknown, but there is a genetic predisposition for the disease. Familial PDB is inherited as an autosomal-dominant trait and several susceptibility loci have been identified. A previous study showed Sequestosome 1 (SQSTM1) mutations in 7 (38.9%) of 18 index patients with familial disease and in 34 of 88 (38.6%) of their relatives in The Netherlands. Currently in the United Kingdom a study is performed in which mutation carriers are randomized to receive zoledronic acid to prevent them from developing PDB, although the rate of carriers developing PDB over time is not exactly known.
Objective
To evaluate the development of PDB after 15 years in subjects from families with familial PDB.
Methods: In total 75 subjects who participated in the previous study, were invited. Participants were first-degree relatives of patients (or when deceased their offspring) and mutation carriers. Serum markers of bone turnover were collected and if increased, subjects were invited to undergo skeletal T99 scintigraphy.
Results
Mean follow-up was 15.9 ±0.32 years and median age was 59 (44-93) years. Of the 23 subjects with increased Alkaline Phosphatase and/or N-terminal propeptide of type 1 collagen that underwent skeletal T99 scintigraphy, 2 were diagnosed with PDB. One, a 74-year-old woman from non-mutation family, had changes compatible with PDB in the pelvic region as showed on combined skeletal scintigraphy/CT-SPECT and a 58 year old man with G425R mutation with PDB of the left calcaneus and L2/L3, which were in retrospect already present in 2002.
Conclusion
After follow-up no new cases of PDB were diagnosed in known SQSTM1 mutation carriers whereas 1 new case was found in a mutation negative family. Only 1 out of 75 (1.3%) subjects with familial disease developed PDB after almost 16 years of follow-up, implying that considering the low incidence, regular screening should not be advised. Since the newly diagnosed patient is from a mutation negative family, these findings hold implications for the counselling of mutation negative families.

O_33

Two-year persistence with Teriparatide improves significantly after extension of an educational and motivational support program

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Objective

To determine whether an educational and motivational support program increases treatment persistence with Teriparatide in the Netherlands.

Methods

In the Netherlands, one central pharmacy provides Teriparatide, enabling us to study persistence in all patients who were prescribed Teriparatide from January 2013 - January 2018. Teriparatide was dispensed as a pre-filled pen containing 750mcg Teriparatide, intended to be used as daily subcutaneous injection of 20mcg Teriparatide for 28 consecutive days. A max. of 26 pens was dispensed during the 24-month treatment period. From January 2013 - April 2015, all patients were instructed and followed according to a basic care program consisting of an intake, educational home visit by a nurse, Teriparatide home delivery, phone calls at 1 week, 2.5 weeks and 8 weeks after treatment initiation. Since May 2015, the basic care program was extended with an educational and motivational support program (patient support program) including a medication adherence scoring tool, an additional phone call at 12 months and motivational letters at 9 and 14 months. The medication adherence scale was aimed at identifying potential non-persistent patients and providing them an additional phone call or home visit to enhance the awareness of the importance of treatment completion. Persistence was defined as the act of continuing the treatment for the prescribed duration, without exceeding the permissible gap (discontinuation up to 28 days). Patients were classified as persistent if 24-26 pens were delivered. The potential 24-month treatment period was evaluated using age and sex adjusted Cox proportional hazard analyses.

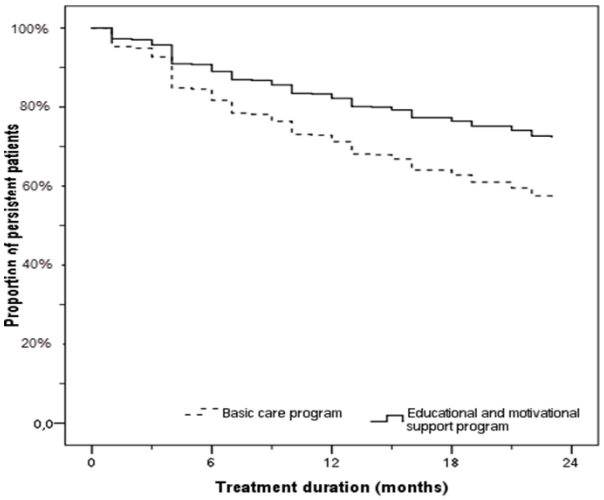
Results

Teriparatide treatment was initiated in 1162 patients: 766 received the basic care program (88% women, mean age 72yrs), and 396 received the support program (84% women, mean age 72yrs). In the basic care group, 2-year persistence was 59% vs. 73% in the support group (p<0.001). Reasons for treatment discontinuation were comparable between both groups, except for discontinuation due to side effects, which was lower in the support group (18% vs 8% respectively, p<0.001). Adjusted analyses showed a reduction of 40% for being non-persistent with the support program compared to the basic care program (HR:0.58 95%CI:0.46-0.72)(Fig.1).

Conclusion

Persistence with Teriparatide significantly improved by the patient support program including the medication adherence scale. The medication adherence scale was able to identify patients who were at risk of treatment discontinuation mainly due to side effects and allowed targeted interventions by a trained nurse resulting in a significant reduction of non-persistence during the 24-month treatment course.

Figure 1: Persistence with Teriparatide per support program



O_34

Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: two-year clinical, structural, and biomarker outcomes

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Background

Knee joint distraction (KJD) is joint-preserving surgery that, like high tibial osteotomy (HTO), postpones total knee arthroplasty (TKA) in younger knee osteoarthritis (OA) patients. One year post-treatment, KJD demonstrated similar clinical outcomes compared to HTO and TKA. This study compares joint space width (JSW) and clinical outcomes for KJD vs. TKA and KJD vs. HTO at two years post-treatment and studies KJD cartilage repair by systemic collagen type II marker evaluation.

Methods

TKA-indicated knee OA patients were randomized to KJD (n=20; KJD_{TKA}) or TKA (n=40). Medial compartmental knee OA patients considered for HTO were randomized to KJD (n=23; KJD_{HTO}) or HTO (n=46). Distraction surgery was performed using two external fixators with springs, placed lateral and medial of the joint. The knee was distracted 5 mm for 6 weeks.

WOMAC questionnaires and VAS pain scores were assessed at baseline (0), 3, 6, 12, 18 and 24 months. In the KJD groups, serum PIIANP and urine CTXII levels, as markers for collagen type II synthesis and breakdown, were determined over time. Normalized Z-indexes were calculated ($Z_{index} = Z_{PIIANP} – Z_{CTXII}$) to express net collagen type II synthesis. The minimum and mean JSW of the most affected compartment (MAC) were measured with KIDA software on standardized radiographs taken at 0, 12 and 24 months.

Results

Of the 129 included patients, 15 patients were lost in the KJD_{TKA} (1), TKA (6), KJD_{HTO} (3), and HTO (5) groups. Statistically significantly improved structural and clinical outcomes were sustained for at least two years post-treatment (figure 1A-C). At 24 months, there were no differences between the KJD_{HTO} and HTO groups (all p>0.120) or between the KJD_{TKA} and TKA group, except for the VAS pain in favor of TKA at 24 months (p=0.016; figure 1B). The collagen type II synthesis (figure 1D) was significantly decreased at 3 months (-0.43±0.20; p=0.035) after which this reversed towards an increase over time (24 months: +0.59±0.18; p=0.003).

Conclusions

Sustained improvement of clinical benefit and JSW increase after KJD is demonstrated for patients with medial compartmental knee OA indicated for HTO or patients with end-stage knee OA indicated for TKA. The cartilage repair observed on radiographs is supported by beneficial change in biomarkers for collagen type II. For the HTO-indicated population, results of KJD and HTO patients were similar. For the TKA-indicated patients, TKA appeared to result in a slightly better clinical outcome, however at the expense of the native knee joint.

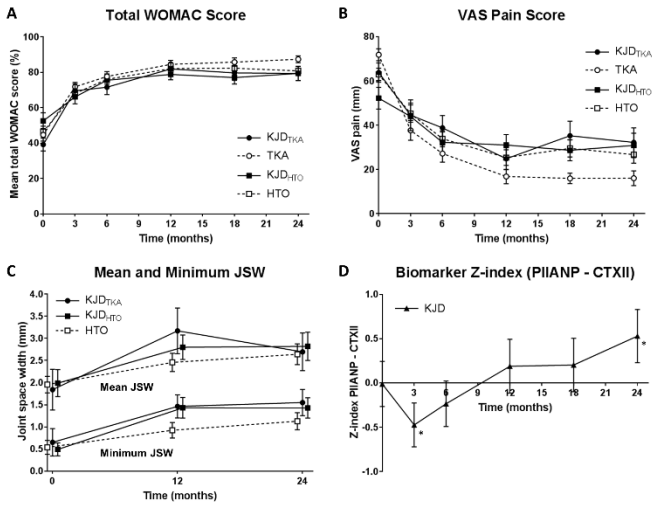

Figure 1 Change in A) total WOMAC score and B) VAS Pain Score after treatment with knee joint distraction (KJD), total knee arthroplasty (TKA) and high tibial osteotomy (HTO). KJD patients are divided in KJD_{TKA} (from the trial including patients for KJD and TKA) and KJD_{HTO} (from the trial including patients for HTO and TKA). C) Change in minimum and mean joint space width (JSW) measured on radiographs after KJD and HTO. D) Biomarker Z-index changes for all KJD patients (KJD_{TKA} and KJD_{HTO} combined) after treatment, indicating net collagen type II synthesis. $Z_{index} = Z_{PIIANP} – Z_{CTXII}$, where the Z-values for both biomarkers are relative to baseline and * indicates statistically significant changes compared to baseline. In all graphs, the mean values ± SEM are given.

O_35

Prevalence of clinical knee and hip osteoarthritis and evolution of symptoms in a primary hand osteoarthritis cohort after 2 year follow-up

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In hand osteoarthritis patients complaints of other joints are relatively common. However, the exact frequency of polyarticular osteoarthritis is not well known.
The objective of this study was to investigate the prevalence of clinical knee and hip osteoarthritis in hand osteoarthritis patients at baseline, and osteoarthritis incidence and change in symptoms after two year follow-up.
Primary hand osteoarthritis patients presenting at the rheumatology outpatient clinic were diagnosed based on rheumatologist opinion and were consecutively included in the HOSTAS (Hand OSTeoArthritis in Secondary care) cohort. In the 538 baseline patients, knee and hip osteoarthritis and presence of joint prosthesis was assessed. In 452 patients data was available after 2 years. Evolution of presence of self-reported pain, development of knee and hip osteoarthritis and incidence of joint prosthesis was investigated. Osteoarthritis was defined by the clinical ACR classification criteria.
In 538 baseline patients (86% women, mean age 61 years), 227 patients (42%) were classified with either clinical knee or hip osteoarthritis, or had a knee or hip prosthesis. Clinical knee osteoarthritis was defined in 181 patients (35%) and 25 patients (5%) had a knee prosthesis. Additionally, 38 patients (7%) were classified with clinical hip osteoarthritis and 22 patients (4%) had a hip prosthesis. In the 452 follow-up patients baseline characteristics were comparable to the entire cohort. At baseline, knee and hip pain was present in 45% and 34% of patients, respectively. Pain fluctuated over time. Knee complaints resolved in 47 and started in 69 patients, and hip pain resolved in 57 and started in 76 patients. Clinical knee osteoarthritis was defined in 147 patients, 24% of patients no longer suffered from knee pain and six progressed to getting knee replacement surgery after 2 years. Clinical hip osteoarthritis was defined in 31 patients, pain resolved in 16% of patients and one patient underwent hip replacement surgery. In the 285 patients without knee osteoarthritis or prosthesis at baseline, incidental clinical knee osteoarthritis was observed in 71 patients (25%) and 3 patients got a knee prosthesis after 2 years. In the 394 patients without hip osteoarthritis or prosthesis, incidental clinical hip osteoarthritis was observed in 24 patients (6%) and 10 patients got a hip prosthesis.
Polyarticular osteoarthritis in primary hand osteoarthritis patients is a common phenomenon. Fluctuations in joint pain occur often, and insight in these fluctuations is important since they may influence fulfilment of the clinical ACR classification criteria.

Table 1. Evolution of knee and hip pain and prosthesis incidence in 452 hand OA patients after 2 year follow-up.

	Evolution over 2 years' time		
	Sustained	**Improvement**	**Incident**
Knee			
No clinical OA at baseline			
Pain at baseline - no	73%		27%
Pain at baseline - yes	79%	21%	
Prosthesis	-	-	1%
Clinical OA at baseline			
Pain at baseline - yes	76%	24%	-
Prosthesis	-	-	4%
Hip			
No clinical OA at baseline			
Pain at baseline - no	75%		25%
Pain at baseline - yes	57%	43%	
Prosthesis	-	-	2%
Clinical OA at baseline			
Pain at baseline - yes	84%	16%	-
Prosthesis	-	-	3%

O_36

2018 updated EULAR recommendations for management of hand osteoarthritis

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Background
Since publication of the European League Against Rheumatism (EULAR) recommendations for management of hand osteoarthritis in 2007 new evidence has emerged.
Objective
To update the EULAR recommendations for management of hand osteoarthritis.
Methods
The EULAR Standardised Operating Procedures were followed. A systematic literature review was performed, collecting evidence regarding all non-pharmacological, pharmacological and surgical treatment options published to date. The results were presented to an international task force of 19 members representing 10 European countries at a one-day meeting. Based on the evidence and expert opinion, overarching principles and recommendations were formulated. Level of evidence, grade of recommendation and level of agreement were allocated to each statement.
Results
Five overarching principles and 10 recommendations were agreed upon. The overarching principles cover treatment goals, information provision, individualisation of treatment, shared-decision making, and the need to consider multidisciplinary and multimodal (non-pharmacological, pharmacological, surgical) treatment approaches. Recommendations 1-3 cover different non-pharmacological treatment options (education, assistive devices, exercises, and orthoses). Recommendations 4-8 describe the role of different pharmacological treatments, including topical treatments (preferred over systemic treatments, topical non-steroidal anti-inflammatory drugs (NSAIDs) being first-line choice), oral analgesics (particularly NSAIDs to be considered for symptom relief for a limited duration), chondroitin sulphate (for symptom relief), intra-articular glucocorticoids (generally not recommended, consider for painful interphalangeal osteoarthritis), and conventional/biological disease modifying anti-rheumatic drugs (discouraged). Considerations for surgery are described in recommendation 9. The last recommendation relates to follow-up.
Conclusion
The presented EULAR recommendations provide up-to-date guidance on the management of hand osteoarthritis, based on expert opinion and research evidence.

Table. 2018 Update of the EULAR recommendations for the management of hand osteoarthritis

Table. 2018 Update of the EULAR recommendations for the management of hand osteoarthritis

	Overarching principles
A.	The primary goal of managing hand OA is to control symptoms, such as pain and stiffness, and to optimise hand function, in order to maximise activity, participation and quality of life
B.	All patients should be offered information on the nature and course of the disease, as well as education on self-management principles and treatment options
C.	Management of hand OA should be individualised taking into account its localisation and severity, as well as comorbidities
D.	Management of hand OA should be based on a shared decision between the patient and the health professional
E.	Optimal management of hand OA usually requires a multidisciplinary approach. In addition to non-pharmacological modalities, pharmacological options and surgery should be considered
	Recommendations
1.	Education and training in ergonomic principles, pacing of activity, and use of assistive devices, should be offered to every patient
2.	Exercises to improve function and muscle strength, as well as to reduce pain, should be considered for every patient
3.	Orthoses should be considered for symptom relief in patients with thumb base OA. Long term use is advocated
4.	Topical treatments are preferred over systemic treatments because of safety reasons. Topical NSAIDs are the first pharmacological topical treatment of choice
5.	Oral analgesics, particularly NSAIDs, should be considered for a limited duration for relief of symptoms
6.	Chondroitin sulphate may be used in patients with hand OA for pain relief and improvement in functioning
7.	Intra-articular injections of glucocorticoids should not generally be used in patients with hand OA*, but may be considered in patients with painful interphalangeal joints**
8.	Patients with hand OA should not be treated with conventional or biological disease modifying anti-rheumatic drugs
9.	Surgery should be considered for patients with structural abnormalities when other treatment modalities have not been sufficiently effective in relieving pain. Trapeziectomy should be considered in patients with thumb base OA and arthrodesis or arthroplasty in patients with interphalangeal OA
10.	Long-term follow-up of patients with hand OA should be adapted to the patient's individual needs

*1a: Systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT; e.g., <80% follow-up); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles". †A: Based on consistent level 1 evidence; B: Based on consistent level 2 or 3 evidence or extrapolations from level 1 evidence; C: Based on level 4 evidence or extrapolations from level 2 or 3 evidence; D: Based on level 5 evidence or on troublingly inconsistent or inconclusive studies of any level. EULAR, European League Against Rheumatism; GoR, grade of recommendation; LoA, level of agreement; LoE, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; randomised clinical trial (RCT).

O_37

Transmembrane TNF signaling through TNF-RI induces SpA-like inflammation, whereas signaling through TNF-RII is crucial for new bone formation

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Background

TNF can drive strictly distinct inflammatory pathologies depending on its expression form. Previously, we have shown that transmembrane (tm) TNF rather than soluble TNF contributes to key pathological features of spondyloarthritis (SpA), including new bone formation [1].

Objective

Delineate the cellular and molecular mechanisms by which selective tmTNF overexpression leads to SpA-like pathology.

Methods

tmTNF tg mice (TgA86) [2] were crossed with TNF-RI or TNF-RII knock out mice. Animals were followed for 100 days for clinical symptoms of arthritis and spondylitis development. Histology was performed at the end of the study on both peripheral and axial joints. Calvarial mouse fibroblasts were cultured in osteogenic conditions. Differentiation towards osteoblasts was analyzed by alizarin red staining, alkaline phosphatase (ALP) staining as well as by qPCR for collagen type I, II, and X, ALP and RUNX2.

Results

Clinical arthritis, visualized by swelling and deformation of front- and hind paws, was observed in 100% of the $tmTNF^{+/WT}$ (>20) as well as in all $tmTNF^{+/WT}xTNF\text{-}RII^{-/-}$ mice (7/7) but not in $tmTNF^{+/wt}xTNF\text{-}RI^{-/-}$ mice (0/9). Histologically, peripheral synovitis, osteitis and enthesitis were observed in all $tmTNF^{+/WT}$ and $tmTNF^{+/WT}xTNF\text{-}RII^{-/-}$ mice, confirming previous findings that tmTNF-mediated synovitis requires the presence of the TNF-RI receptor [2]. Similarly, hunch back formation and crinkled tails were observed in the $tmTNF^{+/WT}$ and the $tmTNF^{+/WT}xTNF\text{-}RII^{-/-}$ mice but not in $tmTNF^{+/WT}xTNF\text{-}RI^{-/-}$ mice. Histology confirmed the presence of inflammatory cellular infiltrates at the edge of the intervertebral units in all $tmTNF^{+/WT}$ tg mice and all $tmTNF^{+/WT}xTNF\text{-}RII^{-/-}$ mice, but not in $tmTNF^{+/wt}xTNF\text{-}RI^{-/-}$ mice. Whereas these data indicate that TNF-RI is required for tmTNF-induced inflammation, it was striking that 50% (10/20) of the $tmTNF^{+/WT}$ versus none (0/7) of the $tmTNF^{+/WT}xTNF\text{-}RII^{-/-}$ mice depicted clear histological signs of endochondral new bone formation. To test whether TNF-RII is involved in pathological new bone formation in this model, calvarial fibroblasts skulls from $tmTNF^{+/WT}$, $tmTNF^{+/WT}xTNF\text{-}RI^{-/-}$, $tmTNF^{+/WT}xTNF\text{-}RII^{-/-}$ or WT were differentiated with osteogenic medium with or without IL-17A. tmTNF overexpressing fibroblasts enhanced the osteogenic differentiation as observed by ALP and alizarin red staining and increased mRNA levels of Collagen type I and ALP compared to WT. This enhancement in osteogenesis was maintained in $tmTNF^{+/WT}xTNF\text{-}RI^{-/-}$-derived fibroblasts but abolished in $tmTNF^{+/WT}xTNF\text{-}RII^{-/-}$-derived fibroblasts.

Conclusion

The SpA-like phenotype in tmTNF tg mice is crucially dependent on TNF-RI to drive peripheral and axial inflammation, but TNF-RII signaling is required to drive the pathological new bone formation under inflammatory conditions.

O_38

Treatment with immune checkpoint inhibitors and the break of B-cell tolerance to autoantigens

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Background

The field of autoimmunity may benefit from the knowledge gained by studying immune checkpoint inhibitors (ICIs). These agents have shown enormous efficacy in oncology by virtue of their ability to (re)activate T-cells to assault cancer cells. This can come at the cost of severe immune-related adverse effects (irAEs) including arthritis, colitis, and endocrinopathies. Since ICI's mode of action is not antigen-specific, we hypothesized that tolerance may be broken not only to tumor antigens but also to autoantigens, leading to the formation of autoantibodies. This development of autoimmunity could be associated with irAEs and also with anti-tumor efficacy.

Objective

To investigate whether patients treated with ICIs develop autoantibodies, and whether this trait is associated irAEs and ICI efficacy.

Methods

In pre- and post-treatment sera of 133 ipilimumab (anti-CTLA4)-treated melanoma patients, we determined 23 common clinical autoantibodies associated with rheumatoid arthritis (RA), autoimmune hepatitis, thyroiditis, Coeliac's disease, adrenal insufficiency, and autoimmune connective tissue diseases (Figure 1). The association between autoantibody development and irAEs (under ipilimumab or subsequent anti-PD-1 therapy), best overall response, and overall survival was investigated.

Results

Autoantibodies developed in 19.2% (19/99) of pre-treatment autoantibody-negative patients (p<0.0001; Figure 1). A non-significant association was observed between development of any autoantibodies and any irAEs: 5/19 (78.9%) patients that developed any autoantibodies had irAEs, versus 46/80 (57.5%) patients that did not develop autoantibodies (OR: 2.92 [95% CI: 0.85 to 10.01]). Predominantly anti-TPO (4.8%, 6/125) and anti-TG antibodies (6.0% , 8/132) developed in patients negative for these autoantibodies at baseline (p=0.03 and p=0.008, respectively). Patients with anti-thyroid antibodies after ipilimumab had significantly more thyroid dysfunction under subsequent anti-PD-1 therapy: 7/11 (54.6%) patients with anti-thyroid antibodies after ipilimumab developed thyroid dysfunction under anti-PD1, versus 7/49 (14.3%) patients without antibodies (OR: 9.96 [95% CI: 1.94 to 51.1]). For most other autoantibodies, including RA-associated antibodies, post-treatment positivity increased only marginally and was not associated with occurrence of irAEs in the organ system related to the autoantibody specificity. Becoming autoantibody positive showed a trend towards better overall survival (HR for all-cause death: 0.66 [95% CI: 0.34 to 1.26]; Figure 2) and therapy response (OR: 2.64 [95% CI: 0.85 to 8.16]).

Conclusions

Breaking of humoral tolerance as measured by development of autoantibodies is relatively common under treatment with ipilimumab and holds promise as a marker of ICI toxicity and efficacy. The nature of the autoantigens towards which tolerance is broken is not reflected in the phenotype of the irAEs.

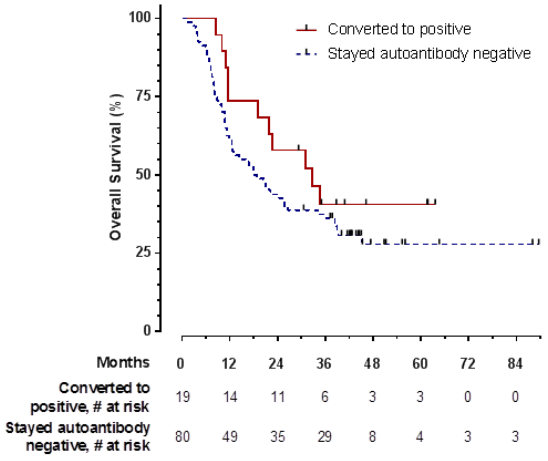

Figure 2: Overall survival for baseline autoantibody negative patients that developed any autoantibodies ("Converted to positive") compared to those that did not develop any autoantibodies ("Stayed autoantibody negative"). Numbers below the graph indicate the number of patients at risk within each group.

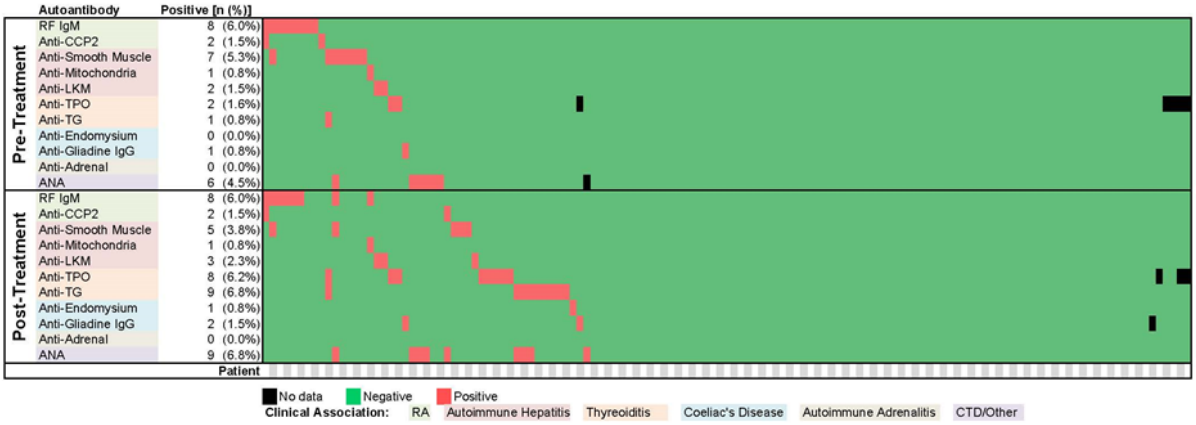

Figure 1. Heatmap of antibody positivity pre- and post-ipilimumab treatment. Not shown: all patients were anti-ENA negative at baseline, while at follow-up, two patients became anti-ENA positive, specifically anti-SSA positive.

O_39

Dominant B cell receptor clones in peripheral blood predict onset of arthritis in individuals at risk for Rheumatoid Arthritis - a validation cohort

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Background

A phase characterized by the presence of specific autoantibodies and arthralgias in the absence of clinically evident synovial inflammation often precedes the onset of rheumatoid arthritis (RA). However, only a subset of these *RA-risk*-individuals will develop active disease in the short term.[1] Recent findings show that dominant B-cell receptor (BCR-)clones in peripheral blood can accurately predict imminent onset of arthritis in these *RA-risk*-individuals.[2]

Objective

To validate the predictive role of BCR-clones in peripheral blood in *RA-risk*-individuals in a larger cohort.

Methods

The BCR repertoire in peripheral blood was analysed using next-generation BCR sequencing in a prospective cohort study of 129 *RA-risk*-individuals from Reade. Like earlier, BCR-clones expanded beyond 0.5% of the total repertoire were labelled highly expanded clones (HECs), shortly referred to as dominant BCR-clones, and individuals were labelled BCR-positive if peripheral blood at study baseline showed ≥5 dominant BCR-clones.

Results

We observed that the number of dominant BCR-clones was increased in *RA-risk*-individuals who developed arthritis within three years, compared to *RA-risk*-individuals who did not 10.6 ± 5.3 vs. 2.2 ± 2.8 (mean±SD; p<0.0001). When creating a ROC-curve we could replicate that the most optimal cut-off for this test is at ≥5 dominant BCR-clones in the peripheral blood (figure 1A), dividing the cohort in 45 BCR-positive-individuals and 84 BCR-negative-individuals. None of the BCR- negative-individuals developed arthritis within 36 months. Within the total follow-up of 104 months only 13% of the BCR-negative-individuals developed arthritis compared to 76% of the BCR-positive-individuals, resulting in a RR of 9.1 (95%>CI 4.4-18.8, p<0.0001).

To test whether a higher number of dominant BCR-clones correlates with higher risk of arthritis BCR-positive-individuals were subdivided into three groups: 5-9 HECs (n=27), 10-14 HECs (n=13) and ≥ 15 HECs (n=5). The Kaplan-Meier curve for all groups is shown in figure 1B (logrank test between BCR-negative-group and positive subgroups: p<0.0001). Having 10 or more HECs corresponded with a PPV of 83% and a NPV of 87% within 3 years. The BCR clonality test clearly added to existing indices of RA risk in *RA-risk*-individuals (data not shown).

Conclusion

In this external validation cohort we could replicate the fact that dominant BCR-clones in peripheral blood predict imminent onset of clinical symptoms of RA in seropositive arthralgia patients with high accuracy. Furthermore, a highly significant association correlating a higher number of dominant BCR-clones with higher risk was shown. We hope these results will support evaluation of early interventions that prevent onset of arthritis.

Figure 1: Predictive value of dominant BCR-clones

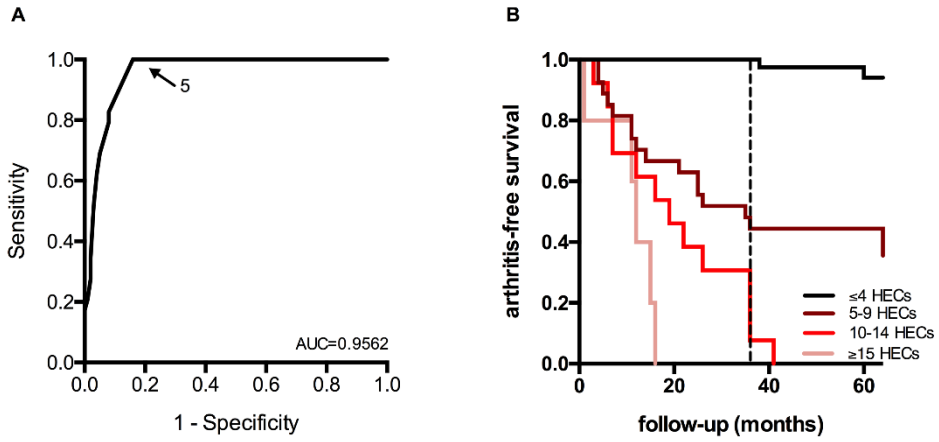

Figure 1 | Predictive value of dominant BCR clones (A) Receiver Operating Characteristic (ROC) curves for the number of dominant clones, in *RA-risk*-individuals (n=129). (B) Kaplan-Meier curve for BCR-positive (divided in sub-groups) and BCR-negative individuals (dotted line at 36 months).

O_40

Disease modifying effects of the canine IL4-10 fusion protein in the canine Groove model of osteoarthritis

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Background
An ideal disease modifying osteoarthritis drug (DMOAD) should have analgesic, chondroprotective and anti-inflammatory effects.
Objective
This study evaluates the DMOAD effects of canine IL4-10FP (cIL4-10FP) in the canine Groove model of OA.

Methods
In 8 skeletally mature mongrels, unilateral knee OA was induced according to the Groove model (right knee). After 6 weeks, dogs were treated weekly with intra-articular injections in the affected knee with PBS (500µl; n=4) or cIL4-10FP (10µg/500µl; n=4) for a period of 10 weeks.
Force plate analysis was used to determine vertical peak force (Fz), braking force (Fy+) and propulsive force (Fy-) in order to evaluate pain. Ratios of right and left hind leg were calculated for each dog. A linear mixed model was used to compare changes 24h after intra-articular injections between PBS and cIL4-10FP.
After 10 weeks dogs were euthanized and cartilage and synovial tissue samples were harvested. Cartilage proteoglycan content and release of proteoglycans were determined *ex vivo* by Alcian Blue assay. Left knees served as controls. Synovial tissue samples were evaluated by histology (HE-staining) to evaluate inflammation.
Results
After OA-induction a clear reduction in Fz and Fy+ was found. Fz (fig. 1) and Fy+ were increased in the cIL4-10FP group compared to the PBS group (p=0.002 and p=0.01, resp.). Fy- showed a similar pattern although not statistically significant.
Proteoglycan content of knees injected with PBS was lower compared to their contralateral controls, representing joint degeneration (27.4mg/g vs 34.3mg/g). In cIL4-10FP injected dogs, proteoglycan content was comparable between both knees (32.9mg/g vs 30.7mg/g). Moreover, mean change in proteoglycan content was higher in the cIL4-10FP group compared to the PBS group (3.9mg/g vs -6.9mg/g; p=0.057, fig.2). A similar pattern was found for release of proteoglycans, which was statistically significant decreased in the cIL4-10FP group compared to the PBS group (0.4% vs 3.0%; p=0.029, fig.2).
Synovial inflammation scores in operated knees were minimally increased (characteristic of this model) and did not differ between both groups (1.85 vs 1.54 for PBS and cIL4-10FP, resp., fig.2).
Conclusions
Dogs treated with cIL4-10FP showed improved Fz and Fy+ compared to PBS treated dogs, reflecting an analgesic effect. Furthermore, improved proteoglycan content and release in the cIL4-10FP treated group indicate a chondroprotective effect. Synovial inflammation was minimal and not different between both groups. These results clearly warrant further research to develop the IL4-10FP towards human application.
This work is supported by the Dutch Arthritis Foundation project NR12-2-202 and LLP22

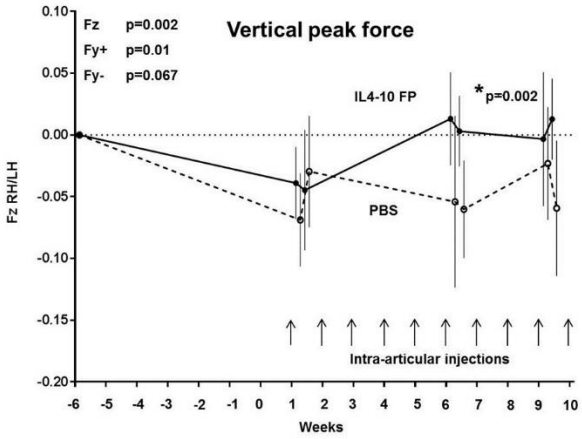

Figure 1. Analgesic effects of cIL4-10 fusion protein
Vertical peak force restored after treatment with cIL4-10FP. Values are presented as mean of four dogs ± SEM. For Fy+ and Fy- p-values are 0.01 and 0.067, respectively.

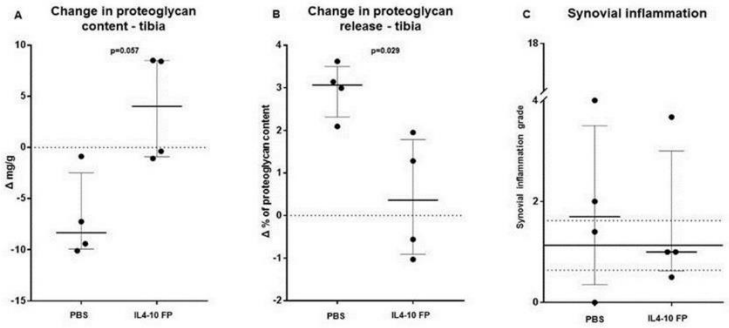

Figure 2. Chondroprotective and anti-inflammatory effects of cIL4-10 fusion protein

A. Change in proteoglycan content between left (control) and right (injected) knees. Values are expressed per animal (dots), representing a mean of 8 samples, and as median ± IQR.

B. Change in release of proteoglycans between left (control) and right (injected) knees. Values are expressed per animal (dots), representing a mean of 8 samples, and as median ± IQR.

C. Synovial inflammation grade of right (injected) knees. Values are expressed per animal (dots) and as median ± IQR. The black line represents the reference value for synovial inflammation grade (± 95%-CI) in knees with OA induction according to the Groove model but without intra-articular injections, based on previous experiments (1.13±0.49; n=9).

O_41

Dynamics of circulating tumor necrosis factor during adalimumab treatment of rheumatoid arthritis using a novel drug-tolerant tumor necrosis factor assay

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Background

Tumor necrosis factor- (TNF) inhibitors are effective in the treatment of rheumatoid arthritis; these include adalimumab, which binds TNF to form inactive complexes. Once in remission, a proportion of patients can successfully discontinue adalimumab treatment, indicating that blocking TNF is no longer necessary for disease control. We developed a novel assay that can quantify TNF in the presence of large amounts of TNF-inhibitor, i.e. a 'drug-tolerant' assay.

Objectives

To investigate, for the first time, the relationship between TNF levels and disease course during adalimumab treatment.

Methods

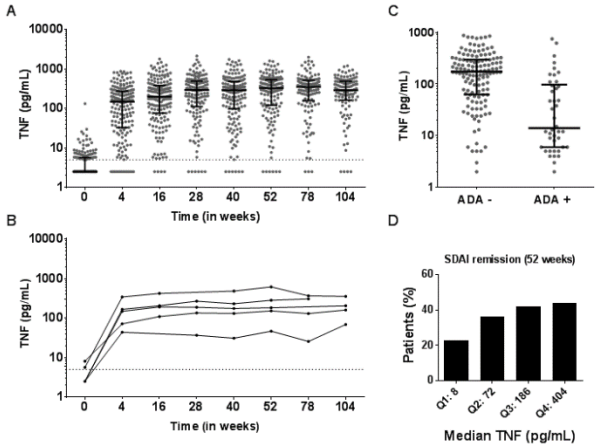
The new drug-tolerant competition enzyme-linked immunosorbent assay was used to quantify TNF levels on initiation and during 2 years of adalimumab treatment in 193 consecutive rheumatoid arthritis patients. The relationship between TNF levels and clinical response was evaluated.

Results

Circulating TNF levels were close to the detection limit at baseline, but TNF levels increased on average >50-fold upon adalimumab treatment (Figure 1A; black lines show median (IQR)), and reached a stable level in time in the majority of patients Figure 1B; representatives of n=193), regardless of disease activity. During treatment, TFN was in complex with adalimumab, and recovered as inactive 3:1 adalimumab:TNF complexes. Remarkably, low TNF levels at week four were associated with a significantly higher frequency of anti-drug antibodies at subsequent time points (Figure 1C), significantly less methotrexate use at baseline, and less frequent remission after 52 weeks (Spearman r = -0.18; p = 0.015; Figure 1D).

Conclusions

TNF levels, in complexed form, do not decline in patients that reach remission, and may therefore not be predictive for treatment discontinuation. However, low complexed TNF levels in the early phase of treatment (wk 4) are strongly associated with anti-drug antibody formation and can be used to identify non-responders in the early phase of treatment.



O_42

Macrophage pet imaging for predicting treatment outcome of de novo rheumatoid arthritis

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Background

Treatment of rheumatoid arthritis (RA) should be initiated as early as possible to prevent further damage. However, clinical assessment of treatment response usually takes 12 weeks or longer. Tools that detect earlier response can improve timely treatment decisions. Positron emission tomography (PET) using the macrophage tracer [11C]-(R)-PK11195 has shown promise for both early diagnosis and monitoring response to therapy in RA patients (1,2).

Objective

To determine the value of [11C]-(R)-PK11195 PET to identify RA responders and non-responders to COBRA-light therapy after 2 weeks of treatment.

Method:

Twenty RA patients (female 10/20, age 54±10 years) with de novo RA based on ACR/EULAR criteria and at least two clinically active joints were included. All patients were given COBRA-light therapy. Clinical evaluations were performed at 0, 2, 4 and 12 weeks of treatment. Whole body [11C]-(R)-PK11195 PET-CT scans were acquired at baseline and 2 weeks of treatment. An experienced reader blinded to clinical data scored the 44 joints of the DAS visually from 0 to 3, creating a cumulative PET score ranging from 0 to 132. PET response was predefined as positive if a decrease in cumulative PET score of ≥ 10% occurred after two weeks. PET outcome was compared with EULAR clinical response at 12 weeks.

Results

After 12 weeks of COBRA-light treatment, 16 out of the 20 patients were classified as EULAR responders (13 ‘good’ and 3 ‘moderate’) and 4 patients as non-responders. At baseline, 134 PET positive lesions were observed in the joints of 20 patients, ranging from 1 to 21 lesions per patient. Lesions were most frequently located in the wrists (figure 1A), small hand joints and small feet joints (19%, 37% and 39% respectively). After 2 weeks of COBRA light treatment, the number of PET positive lesions decreased to 122.

A positive PET response was observed in 13 patients. In 15 of the cases (75%), there was an agreement between the PET response after 2 weeks and EULAR response after 12 weeks (table 1).

Conclusions

Preliminary visual assessment demonstrates the ability of macrophage PET to monitor arthritis activity changes within 2 weeks of treatment. This offers a window of opportunity for development of precision medicine in the early phase of treatment. Future analyses are in progress to assess whether performance can be further improved by quantification of tracer uptake.

References

Gent YY, et al. J Rheumatology. 2014; 41: 2145-52

Gent YY, et al. Arthritis Rheum. 2012; 64: 62-6

Table 1: Correspondence between early PET response and clinical EULAR response.

		EULAR response at 12 weeks	
		Positive	Negative
PET response at 2 weeks	Positive	12	1
	Negative	4	3

Figure 1. PET positive response in the left wrist joint.

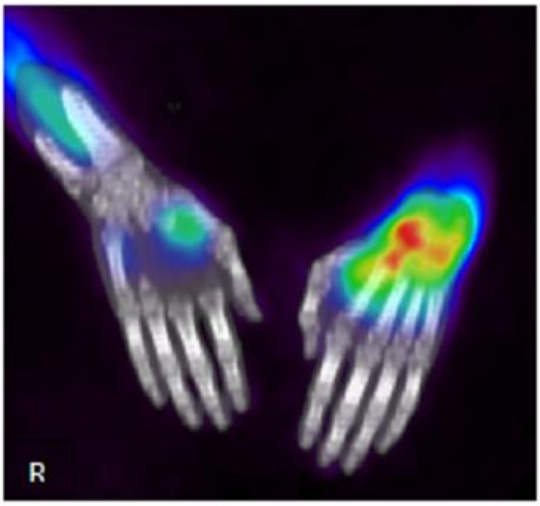

Figure 1A

Figure 1B

O_43

SpA-Net: a disease-specific integrated eHealth system and quality registry for spondyloarthritis in daily practice in the Netherlands

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Background

Regular and personalised monitoring of disease activity, functioning, medication use and side effects is essential to improve and maintain patients' health-related quality of life in spondyloartritis (SpA). Transparency on outcomes and efficiency of care are increasingly demanded, and patient-centeredness is considered essential for quality of care. An integrated eHealth system including an electronic patient medical record (EMR) and real-time quality management system could support these aspects of care.

Objective

To develop and test the usability and acceptability of a disease-specific integrated eHealth system and quality registry for SpA in the Netherlands ('SpA-Net').

Methods

The eHealth system was developed in four phases. First, content and design were discussed with experts in the field of SpA and patients. Second, the database, EMR and quality management system were developed. Third, multiple rounds of testing were performed in collaboration with IT specialists, care providers and patients. Fourth, the eHealth system was implemented in practice, usability and acceptability were tested among patients (semi-structured focus interviews) and care providers (feedback meetings).

Results

SpA-Net was designed and developed in 2015 and implemented in May 2016. All patients entered into SpA-Net have a clinical diagnosis of SpA. Information on domains relevant to clinical record-keeping is prospectively collected at routine outpatient consultations and readily available to care providers. Patients can access an excerpt of these data and complete online questionnaires prior to their visit. The information is presented in graphs wherever possible (Figure). In April 2018, 1204 patients participated in SpA-Net (mean [SD] age 53.8 [14.5] years, 48.3% females). Focus interviews and feedback meetings were held with 16 patients, 9 rheumatologists, and 5 nurses. Patients considered SpA-Net as an accessible system that was beneficial to patient-physician communication and had additional value to current care. Care providers appreciated the additional information for (preparing) consultations. Barriers against use were the initial time required to adopt the EMR and the quantity of data entry.

Conclusion

SpA-Net enables (tele-)monitoring of patients with SpA and optimizes knowledge and communication among patients and care providers. Both considered SpA-Net acceptable and a valuable addition to current care for SpA.

O_44

European League Against Rheumatism recommendations for the role of the nurse in the management of chronic inflammatory arthritis: 2018 update

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Background
In 2012, ten European League Against Rheumatism (EULAR) recommendations for the role of the nurse in the management of chronic inflammatory arthritis have been developed[1]. The recommendations aim to achieve harmonisation in rheumatology nursing care across countries, covering the contribution of rheumatology nurses to the care and management of patients, and additionally cover requirements for their professional performance. During the past years an increasing number of papers with regard to this topic have been published. This justifies an update of the recommendations.

Methods
A systematic literature review was performed in Medline, EMBASE, Cochrane Central, CINAHL, and PsycINFO. In addition the 2016/2017 ACR and EULAR conference abstracts were searched. Results of the literature were shared with a multidisciplinary EULAR Task Force, consisting of 23 persons from 17 European countries, to check for comprehensiveness. Subsequently, a steering committee prepared proposals for update and rewording of the existing recommendations. The proposals were discussed in a one day consensus meeting with the Task Force. Final agreement with the recommendations was obtained by voting after the meeting.

Results
In total, 51 studies were included. Some studies contributed to a higher level of evidence for nurses' contribution regarding patients' satisfaction with care, cost-effectiveness, self-efficacy, the benefit of nurses' extended roles to patient outcomes, as well as structured training aiming at improving nurses' skills. Additional evidence was found for needs-based patient education and telemonitoring. Two recommendations remained unchanged, six were reworded, and two were merged. One recommendation was reformulated as an overarching principle, and two new other overarching principles were formulated. The level of agreement with the recommendations among the Task Force member was high (Table 1).

Conclusions
Three overarching principles and eight evidence- and expert opinion-based recommendations have been formulated, that will provide an up-to-date guidance of nursing care in rheumatology.

References
[1]van Eijk-Hustings Y, van Tubergen A, Bostrom C et al. EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. Ann Rheum Diss. 2012;71(1):13-9.

Table 1

Table 1.
EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis: 2018 Update

	Recommendations	Level of Evidence	Grade of Recommendation	Level of agreement (0-10 mean ±SD)
	Overarching principles			
	Rheumatology nurses are part of a healthcare team			
	Rheumatology nurses provide evidence based care			
	Rheumatology nursing is based on shared decision making with the patient			
1	Patients should have access to a nurse for needs-based education to improve knowledge of CIA and its management throughout the course of their disease	1B	A	10 ± 0,2
2	Patients should have access to nurse consultations in order to enhance satisfaction with care	1A	A	9,7 ± 0,6
3	Patients should have the opportunity of timely access to a nurse for needs-based support; this includes telehealth	1B	B	9,7 ± 0,6
4	Nurses should participate in comprehensive disease management to control disease activity, reduce symptoms, and improve patient preferred outcomes; this leads to cost-effective care	1A	A	9,7 ± 0,5
5	Nurses should address psychosocial issues to reduce patients' symptoms of anxiety and depression	1B	A	9,6 ± 0,7
6	Nurses should support self-management skills to increase patients' self-efficacy	1A	A	9,8 ± 0,4
7	Nurses should have access to and undertake continuous education in the specialty of rheumatology to improve and maintain knowledge and skills	2C	B	9,8 ± 0,7
8	Nurses should be encouraged to undertake extended roles after specialized training and according to national regulations	1A	A	9,7 ± 0,6

O_45

Dutch recommendations for physical therapy in axial spondyloartrhritis (axspa)

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Background

According to the ASAS/EULAR recommendations, physical therapy (PT), especially exercise therapy, is an essential element within the management of axSpA [1]. In the Netherlands considerable variation in the delivery of PT was observed [2], suggesting suboptimal care delivery. This practice variation is likely to be related to the lack of specific recommendations regarding referral, assessment, content, and monitoring of its effectiveness and safety.

Objectives

To develop practice recommendations on PT in axSpA.

Methods

A taskforce of 31 experts was responsible for the recommendations. It consisted of patients (2), rheumatologists (7), physical therapists (13), policy makers (3), researchers (2) and representatives of patient organisations (4). The practice recommendations were based on scientific evidence, expert opinion and patient values and were formulated following a combination of literature review and three expert-group meetings. Clinical questions were formulated in the first expert-group meeting. Then, a systematic literature review was performed to answer the clinical questions. It focused on systematic reviews, meta-analyses and (inter)national guidelines recommendations and consensus statements published after 2010 in English or Dutch. When this approach did not yield sufficient information, relevant RCTs or other types of research designs addressing (one of) the clinical questions were selected. Subsequently, draft recommendations based on the literature, expert opinion and patient values were formulated and discussed in a second meeting. In the third expert group meeting the recommendations were finalized and the level of agreement was determined by a written voting (rating from 1 (total disagreement) to 10 (total agreement)). We defined agreement if at least 80% voted ≥8.

Results

In the first meeting 18 clinical questions were formulated. Six questions pertaining to the content and safety of PT were merged and integrated. In total 12 practice recommendations were formulated on indication(2), referral(2), assessment/monitoring(2), treatment(5), reporting(1) and safety(2) (**Figure 1**). Three recommendations were (partly) based on level 1 evidence (Dutch Evidence Based guidelines, EBRO); others were based on lower levels combined with the opinion of experts written in literature. Agreement was reached for 11 out of 12 recommendations. Mean levels of agreement were high and varied between 8,5-9,1.

Conclusions

Using a standardized process of professional guideline development, 12 practice recommendations for PT management of patients with axSpA were developed. They can guide clinicians and physiotherapists dealing with patients wiht axSpA, ultimately leading to a delivery of a better care. Next steps are the ratification by relevant professional societies as well as dissemination and implementation.

Figure 1

Figure 1: Short description of the content of the Dutch recommendations for physical therapy in axial Spondyloartrhritis (axSpA)	
Indication and referral	
1	Describes indications and reasons for referral to a PT
2	Describes the information that a referral to a PT should contain
Assessment and monitoring	
3	Describes selection of domains, personal and environmental factors that should be assessed at intake and monitoring
4	Describes recommended and optional measuring instruments in the PT assessment
Analysis, objectives, treatment plan, and treatment	
5	Describes on which factors the choice for the duration and form of a PT intervention should be based
6	Describes how a personalized plan should be made and which elements are included (information, education, supervised exercise therapy and planning)
7	Describes the intensity, duration and frequency of the exercise therapy and exercise plan, including monitoring
8	Describes when land or water-based exercise therapy is preferred.
9	Describes which interventions are not recommended in treatment.
Reporting	
10	Describes the information a report from a physiotherapist should contain to give insight in the treatment-effects
Safety	
11	Describes that consideration should be taken to certain comorbidities and axSpA specific aspects that can influence the daily functioning and the therapeutic process and what the contra-indications and PT modalities are
12	Describes information relevant to patients in relation to an increased fracture risk

O_46

Patient factors contributing to and shared decision making in starting/switching biologics in spondyloarthritis

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Background
Biologics are effective for treating symptoms in patients with active spondyloarthritis. Starting/switching specific biologics occurs for various reasons and it is increasingly advocated to involve patients in treatment decisions.
Objectives
To explore which patient-related factors contributed to starting or switching biologics in spondyloarthritis, how patients experienced shared decision making in this process, and to explore the needs of patients starting or switching biologics.
Methods
Patients with spondyloarthritis were recruited from the outpatient department from Maastricht UMC. In semi-structured focus group interviews, patients were asked to elaborate on when and why biologics were started or switched, and if they were involved in treatment decisions. A decision aid for rheumatoid arthritis biologics was shown and patients were asked if they consider a similar decision aid for spondyloarthritis as valuable.
Results
Fourteen patients with spondyloarthritis participated in four focus group interviews. Mean age was 62 years, 10 were female (62.5%). Average time since diagnoses was 28 years. Patients started on average 7.3 years (range 1-14 years) ago with their first biologic. Six patients used one biologic, five patients switched once or twice, and three patients switched more than three times. Factors contributing to starting a first biologic were disease activity, fatigue, intolerance to and ineffectiveness of prior medication. Two patients were included in biological trials. Factors contributing to switching were adverse effects and ineffectiveness of prior biologics.
Most patients were not involved in decision making when biologics were started or could not remember this. Some patients mentioned that only one or limited options were available at the time of start, and that the decision was made by the rheumatologist. Patients underlined the importance of how care providers offer a treatment decision: when initiation or switching was suggested as an option, it was experienced more pleasurable then when the decision was offered as an order.
All patients but one, expressed their wish for a decision aid in which clear information about biologics is provided on mode of administration, interval, and effect on different spondyloarthritis features.
Conclusions
When involving spondyloarthritis patients in shared decision making on starting/switching of biologicals, additional information on effectiveness on disease manifestations, fatigue, adverse events as well as expected duration of effectiveness should be provided. A decision aid can support patients in this.

O_47

Comparison of Physical Activity between patients with different stages of osteoarthritis and the general population: a cross-sectional study

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Background

The benefit of Physical Activity (PA) in different stages of osteoarthritis (OA) is unambiguous considering the positive effects on pain and physical functioning. However, insight in the characteristics of PA (i.e. duration and intensity) between patients in different stages of OA is scarce. Also, comparisons with the general population are understudied.

Objective

To compare the amount (i.e. duration and intensity) of PA in patients in different stages of OA (i.e. patients in primary and secondary care, and post Total Joint Arthroplasty (TJA)) and the general population.

Methods

This study is based on secondary analyses of baseline data from four studies: (1) a study on the effect of an educational program for OA patients in primary care, (2)a study on effectiveness of a multidisciplinary self-management program for generalized OA in secondary care, (3)study among patients whom underwent TJA for end-stage OA in preceding 7-22 months, and (4)a nationwide study among the general population in the Netherlands (N=14,000) on general health. In the current study only patients aged ≥40 years were included. The SQUASH questionnaire was used to assess PA in all 4 studies and to calculate adherence to recommendations, duration (hrs/wk) and intensity (MET.hrs/wk). To compare the amount (hrs/wk) and intensity(MET.hrs/wk) between different stages of OA and the general population, we applied multiple linear regression analysis, adjusted for age, gender and Body Mass Index (BMI).

Results

Demographic characteristics and adherence to PA recommendations are illustrated in Table 1. Mean duration and intensity of PA in the general population were 44.2 hrs/week and 145.7 MET.hrs/week, respectively. Patients after TJA showed higher PA levels (both in terms of duration and intensity) than patients in secondary care as well as the general population(Table 2).

Conclusion

The results of this study show small non-significant differences in PA levels between primary care patients and the general population. Patients after TJA are more physically active than secondary care patients and the general population. However, low adherence rates to PA recommendations indicate the necessity to promote PA in a substantial group of OA patients.

Table 1: Demographic characteristics of three OA groups and the general population in the Netherlands.

	General population N=4448	Primary care N=117	Secondary care N=144	Post TJA N=519
Age (years (SD))	59.2 (11.5)	68.3 (10.4)	59.9 (7.6)	70.1 (9.0)
Gender, % - Female	51.8	59.8	85.4	65.3
Adherence to Dutch PA recommendations(% yes)	68.8	72.6	72.9	76.7

Table 2. Relative difference (%) in mean duration (hours/week) and intensity (MET.hours/week)of PA between groups adjusted for age, gender and BMI.

MET.hrs/week / hrs/week	*General population*	*Primary care*	*Secondary care*	*Post TJA*
General population		0.3 (0.162)	5.4 (0.553)	-5.0* (0.000)
Primary care	1.2 (0.084)		5.1 (0.141)	-5.2 (0.141)
Secondary care	-2.5 (0. 845)	-3.6 (0.141)		- 9.9* (0.000)
Post TJA	5.3* (0.000)	4.1 (0.176)	8.0* (0.000)	

O_48

Running with Rheumatism: a 7-week training programme for novice runners with inflammatory rheumatic disease

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Background
In the Netherlands, running is the second most practised sport. Running is also becoming increasingly popular among people with inflammatory rheumatic diseases, according to the growing number of running-related questions to the Dutch Arthritis Foundation and rheumatologists. Frequently asked questions are: *'Am I allowed to run?'* and *'How can I start in a safe way?'*.

Objectives
Given the increasing demand from the target group, and the potential positive health consequences of high-intensity exercise,[1] we developed a 7-week running programme for novice runners with inflammatory rheumatic disease, and explored its feasibility and safety.

Methods
First we performed a needs assessment among 228 participants with different inflammatory rheumatic diseases. In all, 200 (88%) participants were interested in practicing the sport of running. Then, a rheumatologist, specialized physical therapist, patient representatives and experienced running trainers developed the running programme, based on the proven effective "Start to Run" programme of the Dutch Athletics Federation. The programme aims to prepare participants in 7 weeks for a 20-minute run without breaks, and consists of one supervised group training session and one or two non-supervised training sessions per week. In addition to gradual progression of joint load (by starting with running on soft even surfaces) and running volume, special attention is paid to development of muscle strength and coordination, optimal movement pattern and running at an own comfortable pace. During the programme, the running trainer is in close contact with a rheumatologist and/or specialized physical therapist who can be consulted for advice.

Results
Of the first 29 participants of "Running with Rheumatism", 17 participants completed the programme successfully, 4 participants developed a running related injury, 2 participants dropped out due to rheumatic symptoms, and 6 participants dropped out due to other reasons (e.g. surgery, infectious mononucleosis, burn-out). Participants indicated that they felt safe and comfortable during the group training sessions, and were surprised to be able to achieve so much progress in a short time period. They felt that they had become stronger and got to know their body and physical capabilities better.

Conclusions
The first running groups were successful. The incidence of running related injuries did not significantly differ from incidence rates reported from comparable programmes for regular novice runners in the Netherlands. Therefore, we aim for nationwide implementation.

Piture: Participants of the first running course in Amsterdam in action

O_49

Anakinra for the treatment of acute gout: results of a multicenter, randomized, double-blind, non-inferiority trial in The Netherlands

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Background

For the treatment of gout flares, conventional treatment options as colchicine, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line options in both national and international management guidelines [1,2]. Although generally effective, intolerances to these agents, as well as inefficacies, are seen among gout patients in clinical practice [3]. Alternatives for this subgroup of patients include treatment with an interleukin-1 inhibitor, of which anakinra has not previously been studied in a large double-blind randomized controlled trial [4].

Objective

To evaluate the efficacy and safety of the interleukin-1β receptor antagonist, anakinra, for the treatment of acute gout flares.

Methods

This was a 7-day randomized, double-blind, double-dummy, active comparator controlled trial, conducted at seven hospital centers in The Netherlands. Patients having an acute gout flare, confirmed by the identification of mono-sodium urate crystals, and a pain score ≥ 4 on a Visual Analogue Scale (0-10) were randomized (1:1) to either a five-day treatment with anakinra or treatment as usual (colchicine, naproxen or prednisone). Non-inferiority of anakinra will be established when the change in patient-reported pain in the index joint from baseline to the average of pain scores at day 1, 2, and 3 measured on a 5-point Likert, will not exceed the tolerance limit of 0.4 in favor of treatment as usual. Safety analysis per treatment arm will be compared.

Results

Over the course of two years a total of 88 patients were included in the study. Of these, n=43 (48.9%) received a treatment with anakinra and n=45 (51.1%) treatment as usual. The mean (SD) age of both groups were 63.4 (12.9) and 59.9 (12.7) years, respectively. The majority of patients in both arms were males. No serious adverse events (SAE) were reported for the total group during the seven day trial. Analysis of the non-inferiority of anakinra compared to treatment as usual, as well as additional safety assessment, will follow.

Conclusion

Patient recruitment has finished at all participating centers. Primary outcome results comparing efficacy and safety of anakinra to treatment as usual will be determined in the near future.

Acknowledgements

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O_50

Effectiveness of low-dose radiation therapy on symptoms in patients with hand and knee osteoarthritis: two randomized, double-blinded, sham-controlled trials

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Background

Synovial inflammation has been suggested to play an important role in osteoarthritis (OA). Previous in vitro and in vivo studies of OA in animal models have shown that LDRT exerts anti-inflammatory effects. Low-dose radiation therapy (LDRT) for benign disorders such as knee and hand osteoarthritis (OA) is widely used in some parts of the world. However, a systematic literature review has shown that there is currently insufficient high-level evidence available to indisputably demonstrate the effectiveness in OA patients. Therefore, we conducted two randomized, double-blinded, sham-controlled trials.

Objective

To evaluate the effectiveness of LDRT on symptoms and inflammation in hand or knee OA patients, using two parallel prospective randomized controlled trials (RCTs).

Methods

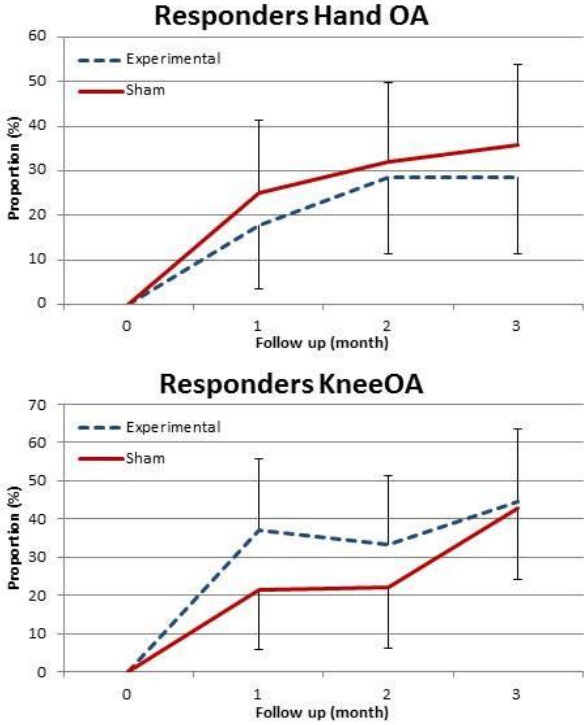
Patients with hand OA (n=56) or knee OA (n=55) fulfilling the clinical American College of Rheumatology criteria, with a pain score ≥ 5/10, non-response to analgesics and exercise therapy were included. We randomly assigned patients 1:1 to receive LDRT (1 Gray per fraction) or sham intervention six times in two weeks, stratified by pain (< 8 versus ≥ 8/10). The primary outcome was the proportion of responders, according to the OMERACT-OARSI responder criteria, 3 months post-intervention. Secondary outcomes included inflammatory signs assessed by ultrasound (US, both hand and knee) and magnetic resonance imaging (MRI, knee only). Logistic and linear regression analyses were used to assess differences in dichotomous and continues outcomes, respectively. Analyses were adjusted for pain stratum.

Results

Baseline characteristics are shown in Table 1. The proportion of responders over time is shown in Figure 1. At 3 months post-intervention, in hand OA, 8/28 patients (29%) in the LDRT versus 10/28 (36%) in the sham group responded (OR 0.7; 95% confidence interval (CI) 0.2-2.2). In knee OA, 12/27 patients (44%) in the LDRT versus 12/28 patients (43%) in the sham group responded (OR 1.1; 95% CI 0.4-3.2). In both hand and knee OA, no differences in any of the clinical outcomes and inflammatory signs were observed.

Conclusion

We found no substantial benefit of LDRT in hand or knee OA patients, neither for the clinical symptoms, nor for the inflammatory signs. Therefore, based on this RCT and the absence of other high-quality evidence, we advise against the use of LDRT as treatment for hand and knee OA. Dutch Trial Register: NTR4574.



	Hand OA		Knee OA	
	LD-RT (n= 28)	**Sham (n= 28)**	**LD-RT (n= 27)**	**Sham (n= 28)**
Male/Female, n	4/24	8/20	12/15	15/13
Age (years)	67 (1)	62 (12)	62 (9)	68 (9)
BMI (kg/m^2)	26 [24–27]	29 [26–31]	29 [25–30]	26 [24–31]
Pain (0-100) #	54 (19)	56 (15)	41 (14)	39 (17)
Functioning (0-100) #	55 (25)	59 (16)	40 (17)	38 (19)
Effusion*	6 [5–8]	5 [3–8]	6 [4–8]	5 [4–7]
Synovial thickening*	3 [1–4]	1 [1–3]	2 [1–3]	2 [1–3]
Power Doppler*	1 [0–2.5]	1 [0–3]	NA	NA
MRI effusion/synovitis (0-12)	NA	NA	5 [3–8]	4 [2–7]

Mean (sd) or median [25% - 75%]; lower scores indicate better health status

#: AUSCAN or WOMAC, respectively; ***** Hand: joint count (0-18), Knee: thickness (mm)

NA: not assessed

Figure 1: Responders over time with 95%CI

O_51

Communiceer meer ; hoe leren AIOS reumatologie goed communiceren en samen beslissen met patiënten? Wat werkt en hoe kunnen we verbeteren?

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Erasmus MC, Rotterdam, Netherlands

Introductie

Er is veel aandacht voor optimaliseren van behandelstrategieën. Maar hoe leren reumatologen eigenlijk om behandelstrategieën optimaal af te stemmen op de patiënt die tegenover hen zit?

Doel Zowel artsen als patiënten vinden goede communicatie en Shared Decision Making belangrijk, maar hoe leer je dit eigenlijk als arts? Praktijkgerichte, actieve communicatie trainingen gecombineerd met feedback zijn het meest effectief[1]. Doel is om in kaart te brengen hoe reumatologen in opleiding denken over Shared Decision Making, hoe vaardig zich zij achten in het bespreken van diagnoses en behandelingen en welke aspecten zij hierbij bespreken. Welke onderwijstechnieken worden gebruikt voor het aanleren van communicatieve vaardigheden, wat werkt en waarom werkt het.

Methode

Reumatologen in opleiding zijn benaderd voor het invullen van een online vragenlijst voor een zelfbeoordeling van communicatieve vaardigheden bij verschillende reumatologische ziektebeelden en vragen over leerstrategieën. Door middel van diepte-interviews met AIOS en opleiders wordt een antwoord gezocht op de vraag wat werkt en waarom werkt dit en wat aanbevelingen zijn voor de opleiding.

Resultaten

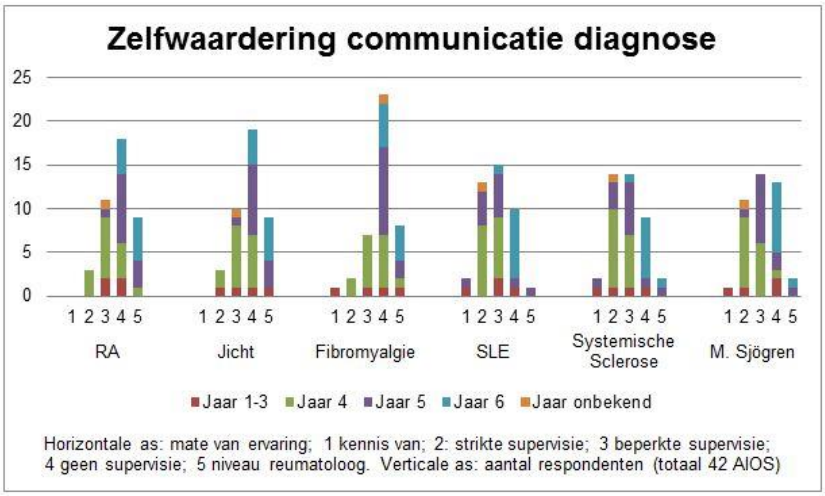
42 AIOS vulden de enquête in; diepte-interviews werden gehouden tot saturatie werd bereikt. AIOS reumatologie vinden Shared Decision Making belangrijk en willen zich hier verder in bekwamen. Zelfbeoordeling communicatiecompetenties volgens VREST laat over alle jaren vergelijkbare scores zien, gemiddeld 3,6 (schaal 1 tot 5). AIOS scoren hun vaardigheden in communicatie over systeemziekten lager vergeleken met andere ziektebeelden (figuur 1), evenals communicatie over behandeling met biologicals versus andere behandelstrategieën. Inhoudelijk wordt met name aandacht besteed aan de medisch inhoudelijke aspecten van diagnose en behandeling en minder aan behandelalternatieven en aspecten zoals werk, sociaal, seksualiteit en zwangerschap (figuur 2).

Er wordt met name geleerd volgens het meester-gezel principe (86%) en daarnaast trial-and-error (83%), waarbij uitleg en bewoordingen van verschillende reumatologen worden overgenomen en toegepast. Patiëntmateriaal (69%) wordt met name aan het begin van de opleiding gebruikt voor het aanleren van begrijpelijke ‘lekentaal’. Meest effectief zijn leersituaties waarbij gerichte feedback werd gegeven over een vooraf geformuleerde duidelijke leervraag naar aanleiding van patiëntsimulatie, video-opname of directe observatie van patiëntcontact. Gezamenlijk spreekuur is zeer leerzaam door de combinatie van ‘modeling’, observatie en feedback gecombineerd. Succes valt of staat met gerichte aandacht voor en feedback op de communicatie.

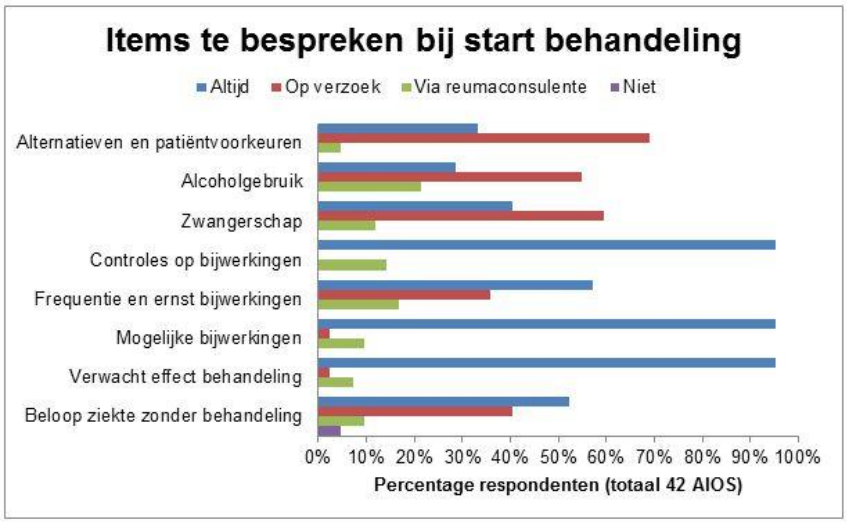
Conclusies

Voor het bekwamen in Shared Decision Making is zowel aandacht voor het verwoorden van medisch inhoudelijke kennis van belang als vaardigheden in het verkennen van waarden van patiënten. Hierin is nog winst te behalen. Gerichte aandacht hiervoor met goede feedback lijkt effectief.

Figuur 1: Zelfwaardering communicatie diverse reumatologische diagnoses



Figuur 2: Aspecten te bespreken bij start nieuwe behandeling


Items te bespreken bij start behandeling
Altijd
Op verzoek
Via reumaconsulente
Niet
Alternatieven en patiëntvoorkeuren
Alcoholgebruik
Zwangerschap
Controles op bijwerkingen
Frequentie en ernst bijwerkingen
Mogelijke bijwerkingen
Verwacht effect behandeling
Beloop ziekte zonder behandeling
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Percentage respondenten (totaal 42 AIOS)

O_52

Hepatitis C screening voor start van een biological

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Introductie

In Netderland vindt screening op het hepatitis C virus (HCV), voor start van biologicals, op grote schaal plaats. De geschatte anti-HCV-prevalentie in Netherlands is echter laag; 0.1-0.4%.[1] Uit oogpunt van doelmatigheid is het de vraag in hoeverre het screenen van alle patiënten zinnig is en of er misschien beter een screening kan plaats vinden aan de hand van een risicoprofiel of levertestafwijkingen. Daarnaast is het vrij onbekend of biologicals inderdaad een reactivatie of exacerbatie van de HCV infectie veroorzaken.

Doel van de studie

Nagaan hoe vaak de diagnose HCV werd gesteld op de afdeling reumatologie van het Franciscus Gasthuis.

Methode

Er werd retrospectief onderzoek gedaan naar de anti-HCV prevalentie op de afdeling reumatologie van het Franciscus Ziekenhuis te Rotterdam, in de periode juni 2010 t/m februari 2018.

Resultaten

Er werd bij 1.445 verschillende patiënten HCV-serologie aangevraagd. Deze bleek in 22 gevallen (1.5%) positief. Zeven patiënten (0.5%) waren chronisch drager van HCV; waarvan zes patiënten (milde) levertestafwijkingen hadden en twee patiënten een voorgeschiedenis van drugsgebruik.
Zes patiënten met HCV antistoffen, werden behandeld met een biological; etanercept, adalimumab of abatacept. Allen hadden bij aanvang een negatieve PCR (geklaarde infectie of status na succesvolle antivirale behandeling). Er deden zich bij deze patiënten geen problemen voor.

Discussie

De anti-HCV prevalentie op de afdeling reumatologie van het Franciscus Gasthuis is hoger dan de geschatte prevalentie in Nederland. Desalniettemin bleek slechts 0.5% chronisch drager.
Uit een studie van Zein et al. bleek dat etanercept naast antivirale behandeling een gunstig effect heeft op de outcome (fibrose en virological response), wat impliceert dat TNF mogelijk een pathofysiologische rol speelt in het geval van HCV infectie.[2] Verschillende caseseries lieten zien dat behandeling met anti-TNF veilig is; er zijn slechts enkele gevallen bekend waarbij een reactivatie optrad. Er is weinig bekend over de veiligheid van andere biologicals.[3]

Conclusie

Op grond van deze data kan beargumenteerd worden om HCV screening alleen nog te doen bij risicogroepen en bij patiënten met levertestafwijkingen. Immers wordt in ons ziekenhuis maar liefst 99.5% onnodig gescreend.

O_53

Ultrasound abnormalities in wrist, MCP2 and MTP5 are most discriminative in predicting arthritis development in seropositive arthralgia patients

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Background

Seropositive arthralgia patients are at risk of developing rheumatoid arthritis (RA). Ultrasound (US) might be used to further predict which seropositive individuals will progress to RA. However, the value of US in the prediction of RA is still a point of debate, mainly due to the use of different scoring systems and compositions of joints in US protocols in literature.

Objective

To investigate which joints are most discriminative in predicting arthritis development in seropositive arthralgia patients.

Methods

We included 174 seropositive patients with arthralgia, but without clinical arthritis. US was performed at baseline in bilateral metacarpal phalangeal (MCP) 2-3, proximal interphalangeal (PIP) 2-3, wrist and metatarsal phalangeal (MTP) 2-3 and 5 joints. Images were scored for grey-scale (GS) synovitis and Power Doppler (PD) on a scale of 0-3. Grades ≥2 for GS synovitis and ≥1 for PD were regarded as abnormal. Clinical arthritis development was assessed in any of 44 joints during yearly follow-up or during an unscheduled visit in case of progression of symptoms, for a maximum of 5 years.

Results

In a total of 2784 joints that were imaged, 112 showed GS synovitis and 14 PD. The majority of GS synovitis was present in MTP2 and MTP3 joints (56 (50%) and 32 (29%), respectively), followed by wrists (15 (13%)), MCP3 (4 (4%)), MTP5 (3 (3%)), MCP2 (2 (2%)) and none in PIPs. Out of joints with PD, 7 were wrists, 3 MTP5, 2 MCP2 and 2 PIP3. Fifty-one (29%) of the patients developed clinical arthritis in ≥1 joint after a median follow-up of 12 (interquartile range 6-23) months. For GS synovitis, the wrist, MCP2 and MTP5 were most discriminative in predicting clinical arthritis development (12/15 (80%) of patients with GS synovitis in wrist developed clinical arthritis, 3/3 (100%) in MTP5 and 2/2 (100%) in MCP2). MTP2 and 3 were least discriminative (<27%). No substantial differences were found between left and right joints. No clear association with clinical arthritis development was found in the limited number of joints with positive PD.

Conclusions

Wrist, MCP2 and MTP5 joints (although numbers were small) showed the highest predictive value for development of clinical arthritis. Although most GS synovitis was observed in MTP2-3, predictive value of MTP2-3 for development of clinical arthritis was low. These results indicate that the choice of joints in the US protocol may influence the predictive value of ultrasound in predicting clinical arthritis development in seropositive arthralgia patients.

O_54

Quantifying the risk of long-term prednisone use on hyperglycemia and diabetes in early rheumatoid arthritis patients; a 10-year sub analysis of the BeSt study

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Background
Glucocorticoids are effective in suppressing disease activity in patients with rheumatoid arthritis (RA), but there are concerns about side effects such as hyperglycemia and diabetes. However, disease activity in RA can also be associated with increases in glucose levels.
Objective
The aim of this study was to assess whether in RA the use of glucocorticoids and the level of disease activity are associated with the development of hyperglycemia and diabetes.
Methods
The BeSt study is a multicenter, assessor-blinded randomized controlled trial in early RA patients. Patients were randomised to 4 treatment groups: 1) sequential monotherapy, 2) step-up combination therapy, potentially escalating to low dose prednisone, 3) initial combination therapy with a tapered high dose prednisone, 4) initial combination therapy with infliximab. We performed a linear regression analysis after 3 months and generalised estimating equations over time with outcomes glucose levels and development of hyperglycemia. Furthermore, we assessed the risk of developing diabetes (by several distinct definitions) by using multiple cox-regression analyses.
Results
In total, 33 patients (6.5%) developed diabetes during the trial; 12 (36.4%) had received any dose of prednisone previous to development of diabetes. Prednisone dose did not influence glucose levels, the odds ratio of hyperglycemia nor the hazard ratio of developing diabetes (table 1). Disease activity was associated with hyperglycemia (OR 1.07, 95% CI 1.01;1.03) and development of diabetes (HR of combined outcome 1.65, 95% CI 1.16;2.33). Over time, an increase of 1 point in DAS was associated with a significant (yet clinically not relevant) increase in glucose level of 0.039 mmol/L.
Conclusion
In early RA patients, prednisone dose did not increase glucose levels, but disease activity was associated with a small increase in glucose level over time. The risk of developing hyperglycemia and diabetes was increased by disease activity, but not by prednisone use. Negative effects of glucocorticoids may be averted through modulation of disease activity.

Table 1. Linear Regression and GEE with outcomes glucose levels, GEE with outcome hyperglycemia over time and cox regressions with outcomes development of diabetes over time, by several definitions

Linear regression, outcome glucose levels at month 3	**β**	**95% CI**
Prednisone dose, unadjusted	-0.003	-0.038 ; 0.031
Prednisone dose, adjusted analysis[1]	*-0.002*	*-0.037 ; 0.033*
Disease activity, unadjusted	0.024	-0.091 ; 0.139
Disease activity, adjusted analysis[2]	0.024	-0.095 ; 0.143
GEE, outcome glucose levels over time	**β**	**95% CI**
Prednisone dose, unadjusted	0.006	-0.008 ; 0.021
Prednisone dose, adjusted analysis[3]	*0.007*	*-0.007 ; 0.021*
Disease activity, unadjusted	0.026	-0.006 ; 0.057
Disease activity, adjusted analysis[4]	0.039	0.005 ; 0.072
GEE, outcome hyperglycemia*	**OR**	**95% CI**
Prednisone dose, unadjusted	0.986	0.953 ; 1.02
Prednisone dose, adjusted analysis[5]	*0.995*	*0.965 ; 1.03*
Disease activity, unadjusted	1.02	0.960 ; 1.09
Disease activity, adjusted analysis[6]	1.07	1.01 ; 1.03
Cox Regression, outcome diabetes (based on glucose*)	**HR**	**95% CI**
Prednisone dose, unadjusted	0.417	0.163 ; 1.07
Prednisone dose, adjusted analysis[7]	*0.400*	*0.155 ; 1.03*
Disease activity, unadjusted	1.32	0.866 ; 2.00
Disease activity, adjusted analysis[8]	1.58	1.02 ; 2.43
Cox Regression, outcome diabetes (with medication)	**HR**	**95% CI**
Prednisone dose, unadjusted	0.868	0.394 ; 1.91
Prednisone dose, adjusted analysis[9]	*0.759*	*0.335 ; 1.72*
Disease activity, unadjusted	1.52	1.01 ; 2.29
Disease activity, adjusted analysis[10]	1.48	0.969 ; 2.28
Cox Regression, outcome diabetes (any of the definitions)	**HR**	**95% CI**
Prednisone dose, unadjusted	0.639	0.314 ; 1.30
Prednisone dose, adjusted analysis[11]	*0.591*	*0.288 ; 1.21*
Disease activity, unadjusted	1.47	1.04 ; 2.07
Disease activity, adjusted analysis[12]	1.65	1.16 ; 2.33

CI: confidence interval, GEE: Generalized Estimating Equations, OR: odds ratio

* hyperglycemia: glucose level above 7.8 mmol/L; diabetes: random glucose level above 11.1 mmol/L at least two time points

[1]: adjusted for baseline glucose, disease activity over time, age, gender and body mass index

[2]: adjusted for baseline glucose, baseline disease activity, prednisone dose, age, gender and body mass index

[3]: adjusted for effect over time, disease activity, age, gender and body mass index

[4]: adjusted for effect over time, prednisone dose, age, gender and body mass index

[5]: adjusted for effect over time, disease activity, age, gender and body mass index

[6]: adjusted for effect over time, prednisone dose, age, gender and body mass index

[7]: adjusted for effect over time, disease activity, age and gender

[8]: adjusted for effect over time, any previous prednisone dose, age and gender

[9]: adjusted for glucose levels over time, disease activity and body mass index

[10]: adjusted for glucose levels over time, any previous prednisone dose and body mass index

[11]: adjusted for effect over time, disease activity, age and gender

[12]: adjusted for effect over time, any previous prednisone dose, age and gender