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ÖGR-ABSTRACTS 2007

JAHRESTAGUNG DER ÖGR 23. UND 24. NOVEMBER 2007 ABSTRACTS DER POSTER UND VORTRÄGE

Klinische Abstracts

01

FRÜHE VERÄNDERUNG DER KRANKHEITSAKTIVITÄT DER RHEUMATOIDEN ARTHRITIS SAGT LANGFRISTIGE THERAPIEERFOLGE VORAUS

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Hintergrund: Rezente Studien zeigten, daß bei der rheumatoiden Arthritis (RA) ein Ansprechen auf antirheumatische Basistherapien frühzeitig evaluiert werden sollte. Üblicherweise wird ein Intervall von 3 Monaten empfohlen. In der vorliegenden Studie untersuchten wir die Wertigkeit der Krankheitsaktivitätsbemessung nach 3 Monaten im Hinblick auf das therapeutische Ansprechen nach einem Jahr.

Methoden: Wir führten Daten aus mehreren klinischen Studien mit einer Dauer von zumindest einem Jahr zusammen. Die Studienarme beinhalteten Therapien mit Methotrexat (MTX), TNF-Inhibitoren (TNFi) sowie deren Kombination (KOMB). Die Studien der frühen RA wurden als Analyseset (n = 1342), jene mit nicht-früher RA als Validierungsset verwendet. Mit Hilfe des „Simplified Disease Activity Index" (SDAI) untersuchten wir Assoziationen der Krankheitsaktivität zu Beginn der Studie und nach 1, 2, 3 und 6 Monaten mit der Krankheitsaktivität nach einem Jahr Therapie. Folgende statistische Methoden wurden verwendet: Spearman-Rang-Korrelation, ANOVA, Diagnostisches Testen (ROC-Kurven-Analyse) und PROBIT-(Regressions-) Analysis.

Resultate: Die Korrelationsanalyse mit dem Einjahres-SDAI war bereits für den Ausgangs-SDAI signifikant ($p < 0{,}0001$), der Koeffizient stieg jedoch auf bis zu $r = 0{,}59$ für den SDAI nach 3 Monaten. Die ROC-Kurvenanalyse der MTX-Patienten zeigte einen Anstieg des diagnostischen Nutzens (Fläche unter der ROC-Kurve: 0,5 = kein Nutzen durch den Test; 1 = perfekter Test) von 0,62 über 0,70, 0,72, 0,78 zu 0,88 für die 1-, 2-, 3- bzw. 6-Monats-Werte des SDAI. Vergleichbare Ergebnisse wurden für die Kombinationsgruppe gesehen. **Abbildung 1** verdeutlicht dieses Ergebnis im Rahmen einer PROBIT-Analyse, welche die Wahrscheinlichkeit, Remission oder niedrige Krankheitsaktivität nach einem Jahr zu erreichen (y-Achse) im Zusammenhang zu den SDAI-Werten nach drei Monaten darstellt. Es zeigten sich für alle Analysen dieselben Ergebnisse, wenn CDAI und DAS28 verwendet wurden.

Schlußfolgerungen: Die erzielte Krankheitsaktivität innerhalb der ersten drei Monate unter antirheumatischer Therapie entscheidet maßgeblich über den therapeutischen Erfolg nach einem Jahr der Therapie. Diese Daten unterstützen Therapiestrategien, die bei Fehlen eines Erfolges nach drei Monaten eine Steigerung der Therapie fordern.

02

DIE RADIOGRAPHISCHE PROGRESSION BEI PATIENTEN MIT ANKYLOSIERENDER SPONDYLITIS – DEFINIERUNG DER ZENTRALEN ROLLE DES SYNDESMOPHYTEN

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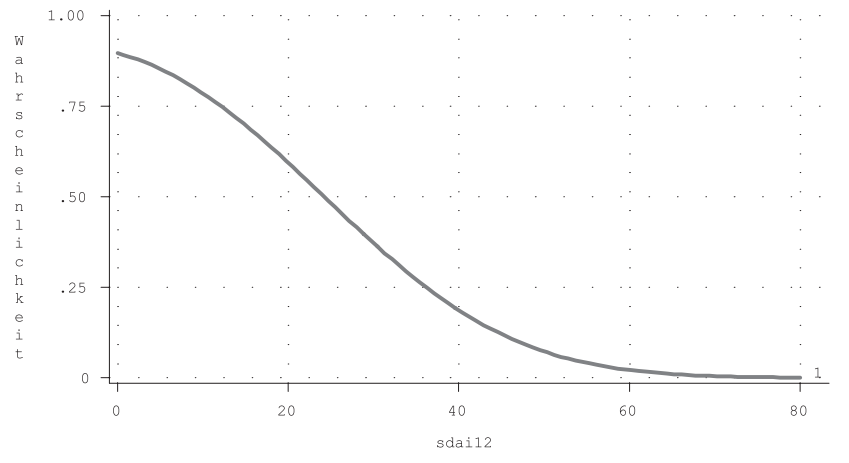
Einleitung: Die augenfälligsten Strukturveränderungen bei Patienten mit AS sind Syndesmophyten und Ankylose. Angesichts der klinischen Wirksamkeit der TNF-Blocker und Fehlen von kontrollierten Vergleichsstudien ist der natürliche Verlauf der radiographischen Progression von besonderem Interesse.

Methoden: Es wurden 146 AS-Patienten (54,3 ± 12 J, KH-Dauer 22,2 ± 12 J) retrospektiv eingeschlossen. Bei allen lagen komplette Röntgenaufnahmen der HWS und LWS zu mindestens zwei Zeitpunkten (Baseline [BL] und Follow-up [FU]) vor. Alle Aufnahmen wurden mittels mSASSS von zwei Readern gescort. „Definitive" Veränderung zu BL war das Vorhandensein von einem Syndesmophyten. „Definitive" Progression war als die Entwicklung eines neuen Syndesmophyten definiert.

Resultate: Der mittlere FU-Zeitraum lag bei 3,8 ± 1,7 Jahren (1–6 J); die mittlere Anzahl von zwei Beobachtungszeitpunkten/Patient war 2,7 (2–6). Der mSASSS lag im Mittel bei 20,6 ± 14,4 zu BL und bei 24,6 ± 15,9 zu FU ($p = 0{,}000$). Die mittlere radiographische Progression nach 2, 4 und 6 Jahren lag bei 4,1 ± 5,4, 5,7 ± 10,1 und 7,8 ± 6,3 Punkten. Die jährliche Röntgenprogression lag im Mittel bei 1,3 mSASSS-Punkten (1,2–2,0 Punkte). Die häufigsten Veränderungen zu BL waren Syndesmophyten und Ankylose (93/146 Pat., 63,7 %), die sich zu FU auf 115/146 Pat. (78,8 %) gesteigert haben. Progression wurde bei 128/146 (79 %) und definitive Progression bei 88/146 Patienten (60 %) beobachtet. Das bedeutet, daß 76 % aller Patienten neue Veränderungen auf der Basis von Syndesmophyten/Ankylose aufwiesen. Syndesmophyten im dorsalen Wirbelkörperbereich waren bei 48 % der Patienten vorhanden, meistens (63 %) in Kombination mit ventralen Veränderungen.

Abbildung 1: Aletaha D et al. Wahrscheinlichkeit einer Remission oder niedrigen Krankheitsaktivität nach einem Jahr Therapie in Abhängigkeit von der Krankheitsaktivität nach 3 Monaten Therapie



Patienten mit definitiven Veränderungen zu BL hatten eine höhere Progression, verglichen zu Patienten ohne definitive Veränderungen (6,9 ± 9,2 vs 4,8 ± 8,5, p = 0,001). Gleichzeitig zeigten Patienten mit Syndesmophyten zu BL häufiger (92/132, 69,7 %) eine definitive Progression, verglichen mit Patienten ohne solche Veränderungen (11/30, 36,7 %), (p = 0,001). Sechs von 18 Patienten (40 %) ohne Veränderungen zu BL zeigten Progression zu FU, davon 4/6 (66,7 %) definitive Veränderungen.

Schlußfolgerung: Die mittlere natürliche radiographische Progression bei AS ohne Biologika lag bei 1,3 mSASSS-Punkten/Jahr. Die mittlere Veränderung nach 4 Jahren (5,7 Punkte) war höher als die der OASIS-Kohorte (4,4). Die meisten AS-Patienten in fortgeschrittenem Stadium haben definitive radiographische Veränderungen; Syndesmophyten und Ankylose kommen am häufigsten vor. Prognostisch ist es bei Patienten mit Syndesmophyten wahrscheinlicher, daß sich im Lauf der Zeit eine weitere radiographische Verschlechterung entwickelt.

03

Die radiographische Progression bei Patienten mit ankylosierender Spondylitis – Definierung der zentralen Rolle des Syndesmophyten

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Einleitung: Strukturelle Veränderungen wie Erosionen, Syndesmophyten und Ankylose sind typische Zeichen für die ankylosierende Spondylitis (AS). Ihre Quantifizierung ist mittels des modifizierten Stokes-AS-Spinal-Score (mSASSS) möglich. Die radiographischen Zeichen, die für die Erfassung zukünftiger struktureller Veränderungen im Sinne von Progression zuständig sind, sind allerdings noch unklar. In dieser Studie analysieren wir die strukturellen Veränderungen von AS-Patienten mittels unterschiedlicher Parameter mit dem Ziel, die aussagekräftigsten Veränderungen im Hinblick auf zukünftige radiographische Progression zu definieren.

Methoden: Konventionelle Rönrgenaufnahmen der Wirbelsäule von 116 AS-Patienten wurden mittels mSASSS zu Baseline (BL) und nach 2 Jahren (FU) evaluiert. Die radiographische Progression wurde ermittelt durch Erfassen von 1. allen Veränderungen, 2. Entstehung von Syndesmophyten/Ankylose („definitive" Veränderung) und 3. Verschlechterung um mehr als den sog. „smallest detectable change" (SDC). Der Cut-off der Wachstumsrichtung von 45° wurde zur Differenzierung zwischen Syndesmophyten und Spondylophyten herangezogen. Der einfache radiographischer Schaden zeigte sich mit dem Score von ≤ 1 und definitiver Schaden mit dem Score von ≥ 2 im mSASSS.

Resultate: Neue Syndesmophyten nach 2 Jahren wurden in 31 % und radiographische Progression (einschl. minimalen Veränderungen) in 42 % der Patienten beobachtet. Dies bedeutet, daß in 74 % der Patienten die radiographischen Veränderungen aufgrund der Bildung von Syndesmophyten oder Ankylose beobachtet wurden. Zum Vergleich: 28 % der Patienten zeigten Veränderungen, wenn der SDC (2 mSASSS-Punkte) als Maß herangezogen wurde.

Keine (mSASSS = 0) oder nur verdächtige (Erosionen, Sklerose, mSASSS = 1) Veränderungen waren zu BL in 59/116 Patienten (50,9 %, 95 % CI: 41,9 %–59,8 %) vorhanden. Definitive radiographische Progression (Bildung von Syndesmophyten/Ankylose, mSASSS = 2 oder 3) nach 2 Jahren wurde bei 11 dieser 59 Patienten (18,6 %, 95 % CI: 10,7 %–30,4 %) festgestellt. Bei den übrigen 57/116 (49,1 %) Patienten mit definitiven Veränderungen zu BL (keine klinischen oder demographischen Unterschiede zu den anderen 59 Patienten) zeigten 25 (43,9 %, 95 % CI: 31,8 %–56,7 %) neue oder zusätzliche Syndesmophyten zu FU. Insgesamt wiesen somit 36/116 Patienten (31 %, 95 % CI: 23,3 %–39,9 %) definitive Veränderungen zu FU auf, unabhängig ihres radiographischen Status zu BL. Ähnliche Ergebnisse zeigten sich bei der Evaluierung einzelner Wirbelkörperkanten.

Patienten mit definitivem radiographischen Schaden zu BL zeigten eine höhere radiographische Progression nach 2 Jahren, verglichen mit Patienten ohne radiographische Veränderungen zu BL (mittlere Veränderung im mSASSS 2,6 ± 4,0 vs. 0,8 ± 1,4, p = 0,002).

Anhand der prädefinierten Wachstumsrichtung von mehr oder weniger 45° könnten nur 12 % aller Osteophyten mit Syndesmophyten verwechselt werden.

Schlußfolgerung: Syndesmophyten und Ankylose sind die am meisten relevanten strukturellen Veränderungen bei der AS, auch im mSASSS. Die Entwicklung allein schon eines neuen Syndesmophyten innerhalb von 2 Jahren kann als Vorbote zukünftiger radiographischer Progression gelten – das ist wichtig für die klinische Tätigkeit. Die Schwere der radiographischen Veränderungen zu BL ist prädiktiv für spätere radiographische Progression, und das Vorhandensein von zumindest einem Syndesmophyten ist am meisten prädiktiv.

04

Anhaltende klinische Wirksamkeit und Sicherheit der Therapie mit Infliximab bei Patienten mit ankylosierender Spondylitis über 6 Jahre

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Einleitung: Die kurzfristige Wirksamkeit der Anti-TNF-Therapie in Patienten mit aktiver ankylosierender Spondylitis (AS) ist bekannt. Es ist weiterhin unklar, ob und für wie lange die Wirksamkeit und Sicherheit dieser Therapie anhält. Hier stellen wir unsere Erfahrungen nach 6jähriger Therapie mit Infliximab bei AS-Patienten vor.

Methoden: Erstmalig wurden 2001 [1] 69 Patienten mit aktiver AS (BASDAI und VAS ≥ 4) in der Studie eingeschlossen (Baseline, BL). Alle Patienten wurden mit Infliximab (5 mg/kg i. v./6 Wochen) behandelt, mit Ausnahme einer kurzen Abbruchphase nach 3 Jahren [2]. Der primäre Endpunkt dieser Verlängerung war der Anteil der Patienten in klinischer Remission anhand der ASAS-Kriterien nach 6 Jahren (FU2), verglichen zu BL und zum Ende des 3. Studienjahres (FU1).

Resultate: Insgesamt haben 43 Patienten das 3. Studienjahr und 38 davon (90,5 %) das 6. Studienjahr beendet (55 % der anfänglichen 69). Partielle klinische Remission war in 14/38 Patienten (36,8 %) zu FU2 vorhanden, ähnlich wie zu FU1. Sieben von 14 (50 %) und 8/14 Patienten (57 %),

die nach 6 Jahren in klinischer Remission waren, zeigten eine klinische Remission bereits 12 Wochen (3 Infusionen) und 24 Wochen (5 Infusionen) nach Therapiebeginn.

Der mittlere BASDAI zu FU2 lag bei 2,4 ± 1,7 (BL: 6,4, FU1: 2,5). Alle anderen klinischen Parameter zeigten ähnliche Verläufe. BASDAI-Werte < 4 waren in 76 % und < 2 in 43 % der Patienten zu FU2, verglichen mit 79 % und 45 % der Patienten zu FU1. Eine Verbesserung des BASDAI > 50 % zu FU2, verglichen zu BL war in 25/38 Patienten (65,8 %) vorhanden, ähnlich wie zu FU1 (24/38 [63,2 %] Patienten). Eine ASAS-20-%- und ASAS-40-%-Verbesserung zu FU2 war in 31 (82 %) und in 23 (61 %) Patienten vorhanden. Ebenfalls war der Anteil der Patienten bei der Analyse der „5-out-of-6"-Kriterien hoch geblieben, verglichen zu Baseline und mit ähnlichen Werten wie bereits zu FU1. Interessanterweise zeigte die Mehrheit der 38 Patienten (n = 22, 58 %) eine ASAS-20-%-Verbesserung zu allen Zeitpunkten zwischen Woche 24 und FU2. Es zeigten sich keine erwähnenswerten Nebenwirkungen während des 6. Therapiejahres mit Infliximab, ähnlich wie in den Jahren zuvor.

Schlußfolgerung: Unsere langfristigen Ergebnisse über 6 Jahre zeigen eine anhaltende Wirksamkeit und Sicherheit der Infliximabtherapie bei den untersuchten AS-Patienten, auch nach einer Phase mit Abbruch und Wiederaufnahme der Therapie. Bei den meisten Patienten zeigt sich eine konstant niedrige Krankheitsaktivität ohne Wirkungsverlust.

Literatur:
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2. Baraliakos X et al. AR&T 2005.

05

Anhaltende klinische Wirksamkeit und Sicherheit bei Patienten mit aktiver ankylosierender Spondylitis nach 4jähriger Therapie mit Etanercept

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Einleitung: Die Therapie mit Etanercept zeigte bereits signifikante kurz- [1] und mittelfristige [2] Wirksamkeit bei Patienten mit aktiver AS und ohne gleichzeitige Therapie mit DMARDs oder Kortikosteroiden. Ebenfalls konnte die Aktivität der Wirbelsäulenläsionen in MRT-Untersuchungen der gleichen Patienten bereits nach 6 Wochen vermindert werden. Wir berichten hier über die klinische Wirksamkeit und Sicherheit nach kontinuierlicher Etanercepttherapie über 4 Jahre.

Methoden: Insgesamt sind seit Beginn der Studie (BL) 30 AS-Patienten eingeschlossen, die mit Etanercept 2 x 25 mg/week s.c. über 12 Wochen behandelt wurden. Gleichzeitige Therapie mit DMARDs oder Steroiden war nicht erlaubt. Es folgte eine Abbruchphase (mittl. Dauer 27 Wochen) und anschließend (n = 26 Pat.), bei erneut hoher Krankheitsaktivität (BASDAI und VAS ≥ 4), die Wiederaufnahme der Therapie über weitere 4 Jahre. Das primäre Endziel war der Anteil von Patienten in klinischer Remission nach 4 Jahren kontinuierlicher Etanercepttherapie. Sekundäre Endziele waren der Anteil von Patienten mit niedriger Krankheitsaktivität sowie die Sicherheit der Etanercepttherapie nach 4 Jahren.

Resultate: Von den 26 Patienten zu BL beendeten 21 (81 %) Woche 102 (FU1) und 18 (69,2 %) Woche 210 (FU2). In der Intention-to-Treat (ITT)-Analyse nach 4 Jahren zeigte sich eine anhaltend gute Wirksamkeit von Etanercept mit 7/21 Patienten (33 %) in partieller Remission (ASAS-Kriterien). Dieser Anteil hat sich statistisch nicht signifikant unterschieden zu FU1 (9/21 Patienten, 42,9 %). Der Anteil der Patienten mit einer niedrigen Krankheitsaktivität (BASDAI-Wert < 4) war ebenfalls gleich zu den vorherigen Zeitpunkten geblieben und lag jeweils bei 56 %. Eine Verbesserung des BASDAI ≥ 50 % war bei 61,9 % der Patienten, eine ASAS-40-%-Verbesserung bei 62 % und eine „5-out-of-6"-Verbesserung bei 66,7 % der Patienten nach 4 Jahren vorhanden. Somit zeigte sich eine gleichbleibende und statistisch nicht unterschiedliche Effektivität der Therapie mit Etanercept auch während der zweiten Hälfte der Studie (Jahre 2–4), verglichen mit den ersten beiden Studienjahren (BL–Jahr 2, dort 66,7 % für BASDAI 50 %, 66,7 % für ASAS 40 % sowie 76,2 % für „5-out-of-6") bei den gleichen Patienten. Die Erfassung der klinischen Parameter zeigte über den ganzen Zeitraum konstant niedrige Werte, signifikant verbessert verglichen mit BL. Nach 4 Jahren lagen die BASDAI-Werte bei 2,7 ± 2,4 (BL: 6,6 ± 1,1, FU1: 2,7 ± 2,4), die BASFI-Werte bei 3,3 ± 2,7 (BL: 5,7 ± 2,0, FU1: 3,2 ± 2,6) und die BASMI-Werte bei 2,3 ± 2,5 (BL: 4,0 ± 2,0, FU1: 2,4 ± 2,2). Die laborchemische Entzündungsaktivität bestätigte die seit Anfang der Studie konstant niedrige Entzündungsaktivität mit CRP-Werten von 8,4 ± 15,8 mg/l zu FU2 (BL: 23,2 ± 17,5) und BSG-Werten von 18,0 ± 22,7 mm/h zu FU2 (BL: 35,8 ± 23,8) (p < 0,001).

Eine zwischenzeitliche Verschlechterung der Krankheitsaktivität wurde bei fast keinem der Patienten beobachtet. Es wurden ebenfalls keine Nebenwirkungen beobachtet, die zum Therapieabbruch geführt haben. Die Häufigkeit der Nebenwirkungsereignisse war nach 4 Jahren niedrig und vergleichbar mit den Ergebnissen nach 2 Jahren, wobei die einfachen Erkältungen die häufigste Nebenwirkung waren.

Schlußfolgerung: Die kontinuierliche Therapie mit Etanercept nach einer Abbruchphase zeigt eine anhaltende klinische Wirksamkeit und Sicherheit auch nach einem langen Zeitraum von 4 Jahren. Eine gleichzeitige Behandlung mit DMARDs und Steroiden ist nicht notwendig. Der Hauptanteil der Patienten fährt mit der Therapie fort und zeigt eine insgesamt niedrige Krankheitsaktivität ohne Zeichen eines Wirkungsverlustes.

Literatur:
1. Brandt J et al. Arthritis Rheum 2003.
2. Baraliakos X et al. AC&R 2005.

06

Performance of referral recommendations for axial spondyloarthritis in patients with chronic back pain in primary care

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Background: Between first symptoms and making a diagnosis of ankylosing spondylitis (AS) there is still a delay of 5–7 years. This often results in unnecessary diagnostic procedures and inadaequate treatment. Moreover, new effective treatments such as TNF-α blocking agents have become available for active disease. These facts emphasize the need for easy to apply referral parameters for primary care physicians in patients with suspected early AS [1].

Objective: To determine which of the proposed screening parameters or combination of parameters are most useful among primary

care physicians for referral of patients with suspected axial spondyloarthritis (SpA) (AS and early AS at the preradiographic stage) to make a diagnosis of AS [2].

Methods: Primary care physicians in private practice in Berlin were asked to refer patients with chronic low back pain (duration > 3 months) and onset of back pain at an age < 45 yrs to a specialized rheumatology outpatient clinic for further diagnostic work-up if at least one of the following screening parameters were present: 1) inflammatory back pain (IBP), or 2) positive HLA-B27. In addition, sacroiliitis as detected by imaging (either radiography or MRI) could also be a reason for referral because imaging procedures are often performed in primary care anyway, although they were not recommended for screening.

Results: To date 528 cases (mean age 41.3 years, 47.7 % males) were collected. Of these, 42.2 % of patients were referred with only one parameter (16 % HLA-B27+, 14.4 % IBP+, 8 % sacroiliitis by imaging, 4 % other reasons) and 48.7 % of patients were referred with more than one parameter being positive (17.6 % HLA-B27+ plus IBP+, 9.5 % HLA-B27+ plus sacroiliitis by imaging, 7.2 % IBP+ plus sacroiliitis by imaging, 1.1 % IBP+ plus other reasons, 9.1 % HLA-B27+ plus IBP+ plus sacroiliitis by imaging). 9.1 % were referred without any assessed referral parameter.

In total 43.6 % of all referred patients (mean age 37.3 years, 55.2 % males) were diagnosed of having an axial SpA comprising AS/early AS using these screening parameters. If only one parameter was positive, a diagnosis of AS/early AS was made in 31.4 % of referred patients compared to making a diagnosis in 60.3 % of patients if more than one parameter were positive. The combination of HLA-B27+ plus sacroiliitis by imaging and HLA-B27+ plus IBP+ had the highest probability to result in a final diagnosis of AS/early AS. 47.8 % of patients (n = 110/230) had an early form of AS without the presence of radiological sacroiliitis.

Conclusions: The proposed referral parameters have proven useful for primary care physicians in identifying patients with AS/early AS among young to middle-aged patients suffering from chronic low back pain.

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07

Clinical tests for sacroiliitis and spinal mobility – no helpful tools for diagnosing axial spondyloarthritis (SpA) early

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Background: Chronic inflammatory low back pain and reduced spinal mobility are hallmarks of axial SpA and part of the clinical criteria of the modified New York criteria for ankylosing spondylitis (AS) [1]. The value of clinical tests for sacroiliitis and spinal mobility for diagnosing axial SpA at an early stage has not been investigated.

Purpose: To assess the diagnostic value of clinical tests for pain in the sacroiliac joint (SIJ), and for spinal mobility in patients with undiagnosed chronic back pain.

Methods: Following a screening program for axial SpA, patients with undiagnosed chronic low back pain and age at onset < 45 yrs were referred to a specialized rheumatology outpatient clinic for further diagnostic work-up [2]. A final diagnosis (axial SpA or mechanical low back pain [mLBP]) was made according to expert opinion. Clinical tests for sacroiliitis comprising pain on pressure over SIJ, Mennell-test (maximal flexion of one hip and hyperextension of the other), and Patrick-test (maximal flexion, abduction and external rotation of the hip joints) and tests for spinal mobility (Schober test [pathological if < 4 cm] and lateral lumbar flexion [pathological if < 10 cm]) were performed.

To date 480 cases were enrolled in the program. Of these, tests for pain in the SIJ and spinal mobility were assessed in 244 patients. A diagnosis of axial SpA comprising established AS and pre-radiographic axial SpA was made in 44.3 % of all referred patients while 55.7 % were diagnosed as non-SpA (mLBP). Mean disease duration in patients diagnosed as pre-radiographic axial SpA without definite radiographic sacroiliitis (n = 50, 20.5 %) was 4.7 yrs, in established AS (n = 58, 23.8 %) 13.2 yrs, and in mLBP (n = 136, 55.7 %) 10.5 yrs.

Results: The discriminative capacity was poor for all clinical tests in patients with pre-radiographic axial SpA compared to mLBP (positive likelihood ratios [LR+] 1.1–1.6). In AS, only lateral lumbar flexion provided some discriminative information (LR+ 2.8).

Conclusions: Clinical tests for sacroiliitis do not play a role in diagnosing early axial SpA.

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08

Similar clinical presentations in radiographic (established) and pre-radiographic (early) axial spondyloarthritis (SpA)

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Background: Diagnosing axial spondyloarthritis (SpA) early is necessary to avoid unnecessary diagnostic procedures and to start an optimal treatment early [1]. More data about the characteristics of pre-radiographic (early) axial SpA are needed.

Objective: To compare clinical characteristics of patients with radiographic (ankylosing spondylitis, AS) and pre-radiographic axial SpA who have been newly diagnosed.

Methods: Following a screening program for axial SpA [2], patients with chronic low back pain (duration > 3 months) and onset of back pain at an age < 45 yrs were referred to a specialized rheumatology outpatient clinic for further diagnostic work-up if in addition at least one of the following screening parameters were present: 1) inflammatory back pain (IBP), 2) positive HLA-B27, 3) sacroiliitis as detected by imaging [1]. A diagnosis of axial SpA or non-SpA was made according to expert opinion. Patients with axial SpA were further divided into radiographic and pre-radiographic axial SpA according to the presence of definite radiographic sacroiliitis.

Results: 230 (43.5 %) of 528 collected cases were diagnosed as axial SpA. Out of these 230 patients 110 (47.8 %) were classified as pre-radiographic axial SpA without radio-

graphic sacroiliitis and 120 (52.2 %) as established AS.

Positivity for HLA-B27 and presence of IBP were similar for pre-radiographic axial SpA and AS patients as well as the percentage of males (51.8 % and 58.3 %, respectively). Heel enthesitis, a positive family history of SpA and peripheral oligoarthritis were the most frequent features in both groups. Heel enthesitis, dactylitis and peripheral oligoarthritis occurred more often in pre-radiographic axial SpA patients than in established AS whereas uveitis was more frequent in patients with established AS.

Acute phase reactants were significantly ($p = 0.012$) more often elevated in AS (62.7 %) compared to pre-radiographic axial SpA (45.9 %). The disease activity index BASDAI was the same in both groups (4.0), the functional index BASFI was slightly lower (better function) in pre-radiographic axial SpA (2.9) than in AS (3.3).

Conclusion: Most of the clinical and demographic parameters including the clinically defined disease activity index BASDAI occurred in a similar frequency in established AS and pre-radiographic axial SpA. This indicates that axial SpA patients with or without radiographic sacroiliitis belong to the same spectrum of disease.

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Infliximab verbessert die Wirbelsäulenmobilität bei Patienten mit Spondylitis ankylosans: 2-Jahresergebnisse der ASSERT-Studie

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Einleitung: Die Einschränkung der Wirbelsäulenmobilität ist eines der Hauptmerkmale der Patienten mit AS. Frühere Studien haben gezeigt, daß Wirbelsäulenunbeweglichkeit mit funktioneller Behinderung, beeinträchtigter Lebensqualität und einem Verlust der Leistungsfähigkeit assoziiert ist. Ziel dieser Analyse war es, den Effekt der Langzeitbehandlung mit Infliximab auf die Wirbelsäulenmobilität von AS-Patienten zu untersuchen.

Methoden: ASSERT war eine Phase-III-, doppelblind-randomisierte, placebokontrollierte Multicenter-Studie zur Beurteilung der Wirksamkeit und Verträglichkeit von Infliximab bei Patienten mit aktiver AS. Die Patienten wurden im Verhältnis 8:3 randomisiert und erhielten Placebo- (n = 78) oder Infliximabinfusionen (5 mg/kg Körpergewicht; n = 201) in den Wochen 0, 2 und 6 und danach alle 6 Wochen. In Woche 24 wechselten die Patienten der Placebogruppe zu dem 5 mg/kg Infliximabregime. Ab Woche 36, und fortlaufend bis Woche 96, wurde bei den zu Beginn in die Infliximabgruppe randomisierten Patienten die Dosis auf 7,5 mg/kg Körpergewicht erhöht, wenn sie bei zwei aufeinanderfolgenden Visiten einen BASDAI-Wert von 3 oder mehr aufwiesen. Bei allen Patienten wurde eine Endauswertung in Woche 102 durchgeführt. Zur Erfassung des Bewegungsumfangs wurden der BASMI (Wertebereich von 0 bis 10) und die Brustkorbexpansion gemessen. Eine klinisch bedeutsame Verbesserung wurde als eine Veränderung von ≥1 im BASMI-Score definiert. Die Veränderungen der Behandlungsgruppen wurden mittels ANOVA der Van-der-Waerden-Scores verglichen.

Resultate: Bei den Baselinewerten des BASMI und der Brustkorbexpansion bestanden zwischen den Patientengruppen keine signifikanten Unterschiede. Im Vergleich zur Placebogruppe erzielten Infliximab-behandelte Patienten in Woche 24 eine größere Verbesserung des BASMI-Scores (–0,7 vs. –0,2; $p = 0,02$) und der Brustkorbexpansion (43,6 % vs. 18,7 %, $p = 0,03$). Eine klinisch bedeutsame Verbesserung im BASMI-Score erreichten 51 % der Infliximab-behandelten und 31 % der placebobehandelten Patienten ($p < 0,01$). Darüber hinaus zeigten Infliximab-behandelte Patienten eine graduelle Verbesserung des BASMI und der Brustkorbexpansion nach Woche 24, die bis Woche 102 aufrechterhalten wurde. Die Patienten der Placebogruppe zeigten nach dem Wechsel auf Infliximab in Woche 24 bei Evaluierungen in den Wochen 54, 78 und 102 ähnliche Verbesserungen des BASMI-Scores und der Brustkorbexpansion wie die Patienten der Infliximabgruppe.

Schlußfolgerung: Die Behandlung mit Infliximab führt zu einer klinisch bedeutsamen und anhaltenden Verbesserung der Wirbelsäulenmobilität bei Patienten mit AS.

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Anhaltende Verminderung der Wirbelsäulenentzündung bei Patienten mit Spondylitis ankylosans unter Behandlung mit Infliximab

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Einleitung: Ziel der Arbeit war die Ermittlung der Wirksamkeit Infliximabs auf die Entzündung der Wirbelsäule bei Patienten mit Spondylitis ankylosans durch Magnetresonanztomographie (MRT)- Messungen nach 2jähriger Behandlung.

Methoden: Die Patienten wurden im Verhältnis 8:3 in zwei Behandlungsarme randomisiert. Die Patienten erhielten Infliximabinfusionen (5 mg/kg Körpergewicht; n = 201) oder Placeboinfusionen (n = 78) zum Zeitpunkt 0 und nach 2, 6, 12 und 18 Wochen. In Woche 24 wechselten die Patienten der Placebogruppe zu dem 5 mg/kg Infliximabregime, beginnend mit Infusionen in den Wochen 24, 26, 30 und anschließend alle 6 Wochen bis Woche 96. MRT-Aufnahmen der Wirbelsäule (T1-gewichtete Sequenz vor und nach Gadolinium-Gabe sowie TIRM-Sequenz) wurden bei Baseline sowie in den Wochen 24 und 102 angefertigt. Die Aufnahmen wurden von zwei Personen getrennt ausgewertet. Die zeitliche Abfolge der Aufnahmen sowie die Zugehörigkeit der Patienten zu den Behandlungsarmen waren verblindet. Die Auswertung erfolgte gemäß dem „Ankylosing Spondylitis MRI spinal score for activity" (ASspiMRI-a).

Resultate: Die MRT-Aktivitätsscores sind in **Tabelle 1** zusammengefaßt. Patienten in der Infliximabgruppe zeigten in Woche 24 eine Verbesserung der MRT-Aktivitätsscores, welche bis Woche 102 aufrechterhalten wurde. Patienten in der Placebogruppe zeigten in Woche 24 keine Veränderung der MRT-Aktivitätsscores, diese verbesserten sich aber nach der Umstellung auf Infliximab.

Schlußfolgerung: MRT-Messungen zeigten bei mit Infliximab behandelten Patienten eine über 2 Jahre anhaltende Verminderung der Wirbelsäulenentzündung.

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Verbesserung der Hämoglobinwerte bei Patienten mit Spondylitis ankylosans unter Behandlung mit Infliximab

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Einleitung: Aus früheren Untersuchungen ist bekannt, daß Patienten mit AS eine schlechte körperliche Funktion und schwere Müdigkeit aufweisen und daß sich diese Krankheitsfolgen bei Behandlung mit Infliximab signifikant verbessern. Ziel dieser Arbeit war es, die Wirkung der Infliximabtherapie auf Anämie und die Assoziation der Verbesserung der Hämoglobinwerte (Hgb) mit der Verbesserung der Müdigkeit und körperlichen Funktion zu untersuchen.

Methoden: ASSERT war eine doppelblind-randomisierte AS-Studie. Die Patienten wurden im Verhältnis 3:8 randomisiert und erhielten Placeboinfusionen (n = 78) oder Infliximabinfusionen (5 mg/kg Körpergewicht; n = 201) in den Wochen 0, 2 und 6 und danach alle 6 Wochen. Müdigkeit wurde mittels visueller Analogskala (0–10) ermittelt. Die körperliche Funktion wurde mittels „Bath Ankylosing Spondylitis Functional Indices" (BASFI; 0–10) bewertet. Anämie wurde nach WHO-Kriterien definiert (Hgb < 12 g/dL für Frauen und < 13 g/dL für Männer). Die Besserung dieser Kriterien von Baseline bis Woche 24 wurde zwischen Infliximab-behandelten und placebobehandelten Patienten verglichen. Der Zusammenhang der Verbesserung des Hgb mit Müdigkeit und körperlicher Funktion wurde mittels Spearmans-Korrelation oder multipler Regressionsmodelle getestet, wobei für demographische Kriterien und Krankheitsaktivität adjustiert wurde.

Resultate: Bei Baseline präsentierten sich 18,7 % der Patienten mit einer Anämie (28 % der Frauen und 16 % der Männer). Verglichen mit der Placebogruppe zeigten Patienten aus der Infliximabgruppe in Woche 24 eine statistisch signifikante Verbesserung der Hgb-Werte (0,72 g/dL vs. –0,26 g/dL, $p < 0,001$), der Müdigkeitswerte (2,4 vs. 0,4, $p < 0,001$) und des BASFI (2,1 vs. 0,2). 70,3 % der mit Infliximab behandelten Patienten mit Baseline-Anämie zeigten eine Verbesserung von ≥ 1 g/dL im Hgb-Wert in Woche 24 verglichen mit 8,3 % der mit Placebo behandelten Patienten mit Baseline-Anämie ($p < 0,001$). 70 % der Patienten mit Baseline-Anämie waren nach der Behandlung mit Infliximab nicht mehr anämisch, verglichen mit 25 % in der Placebogruppe. Der Hgb-Spiegel war signifikant mit Müdigkeit und körperlicher Funktion assoziiert. Eine Verbesserung der Hgb-Werte in Woche 24 korrelierte statistisch signifikant mit einer Verbesserung der Müdigkeit ($r = 0,33$, $p < 0,001$) und der körperlichen Funktion ($r = 0,45$, $p < 0,001$). Nach Anpassung an Alter, Geschlecht, Krankheitsdauer und Verbesserung der Krankheitsaktivität war eine Verbesserung der Hgb-Werte noch mit einer Verbesserung der körperlichen Funktion assoziiert ($p < 0,01$).

Schlußfolgerung: Anämie ist eine häufige Komorbidität bei Patienten mit AS, welche mit schwerer Müdigkeit und körperlicher Behinderung assoziiert ist. Die Behandlung mit Infliximab kann Anämie, Müdigkeit und körperliche Funktion signifikant verbessern.

Tabelle 1: Braun J et al.

	Placebo	**Infliximab**
Baseline	n = 77	n = 200
Mittelwert ± SD	6,21 ± 7,95	5,91 ± 6,58
Median (IQR)	4,00 (0,00; 9,50)	3,57 (0,25; 9,00)
Δ BL–Woche 24	n = 72	n = 195
Mittelwert ± SD	0,38 ± 3,97	–4,44 ± 6,16
Median (IQR)	0,25 (–2,50; 2,75)	–2,00 (-8,00; 0,00)
Δ BL–Woche 102	n = 60	n = 161
Mittelwert ± SD	–4,89 ± 6,85	–4,87 ± 6,42
Median (IQR)	–1,00 (–8,75; 0,00)	–2,00 (–8,50; 0,00)

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Schnelle, anhaltende und klinisch bedeutsame Verbesserung der körperlichen Funktion und Arbeitsfähigkeit bei Patienten mit Spondylitis ankylosans unter Behandlung mit Infliximab über 2 Jahre

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Einleitung: Patienten mit AS weisen eine signifikante Einschränkung ihrer körperlichen Funktion und eine Verminderung ihrer Arbeitsfähigkeit auf. Ziel dieser Arbeit war die Untersuchung des Effekts der Langzeitbehandlung mit Infliximab (IFX) auf die körperliche Funktion und Leistungsfähigkeit von AS-Patienten auf Basis der ASSERT-2-Jahresdaten.

Methoden: ASSERT war eine Phase-III-, doppelblind-randomisierte, placebokontrollierte Studie zur Beurteilung der Wirksamkeit und Verträglichkeit von IFX bei Patienten mit aktiver AS. Die Patienten erhielten Placebo- (PLZ; n = 78) oder IFX-Infusionen (5 mg/kg KG; n = 201) in den Wochen 0, 2 und 6 und danach alle 6 Wochen. In Woche 24 wechselten die Patienten der PLZ-Gruppe zu dem 5 mg/kg IFX-Regime, beginnend mit Infusionen in den Wochen 24, 26, 30 und anschließend alle 6 Wochen bis Woche 96. Bei allen Patienten wurde eine Endauswertung in Woche 102 durchgeführt. Die körperliche Funktion wurde mittels BASFI (1–10) erfaßt. Die Auswirkung der Erkrankung auf die Arbeitsfähigkeit wurde mit einer visuellen Analogskala (0–10) ermittelt. Veränderungen des BASFI und der Arbeitsfähigkeit der Behandlungsgruppen wurden mittels ANOVA der Van-der-Waerden-Scores verglichen.

Resultate: Bei Baseline gab es keine Unterschiede zwischen den Gruppen. Bereits in der 2. Woche konnte in der IFX-Gruppe eine deutlichere Verbesserung des BASFI-Scores im Vergleich zur PLZ-Gruppe festgestellt werden ($p < 0,001$). In Woche 24 erreichten 48 % der Patienten der IFX-Gruppe eine klinisch bedeutsame Verbesserung des BASFI (≥ 2) gegenüber 13 % der Patienten

der PLZ-Gruppe ($p < 0,001$). Die mittlere Veränderung (SD) in Woche 24 war 2,1 (2,2) bei IFX-Patienten und 0,2 (1,7) bei PLZ-Patienten. IFX-behandelte Patienten zeigten nach Woche 24 eine graduelle Verbesserung des BASFI, die bis Woche 102 aufrechterhalten wurde. Die Patienten der PLZ-Gruppe zeigten nach dem Wechsel auf IFX bei Evaluierungen in den Wochen 36, 54, 78 und 102 ähnliche Verbesserungen des BASFI-Scores wie die Patienten der IFX-Gruppe. Die aktiv berufstätigen Patienten der IFX-Gruppe erzielten in Woche 24 eine größere mittlere Verbesserung der täglichen Leistungsfähigkeit als die der PLZ-Gruppe (1,9 vs. 0,7; $p = 0,03$). Diese Verbesserung wurde bis Woche 102 aufrechterhalten. In Woche 102 war die Verbesserung der Leistungsfähigkeit in beiden Gruppen vergleichbar. Sie korrelierte zu allen Zeitpunkten signifikant mit der Verbesserung der körperlichen Funktion ($p < 0,01$).

Schlußfolgerung: Infliximab-behandelte AS-Patienten zeigten über 2 Jahre eine schnelle, substantielle und anhaltende Verbesserung der körperlichen Funktion und täglichen Leistungsfähigkeit.

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Keine Hemmung der radiographischen Progression bei Patienten mit Spondylitis ankylosans durch 2jährige Behandlung mit Infliximab

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Einleitung: Ziel der Arbeit war die Ermittlung der Wirksamkeit Infliximabs auf die radiographische Progression bei AS-Patienten der ASSERT-Studie.

Methoden: 201 Patienten erhielten Infliximabinfusionen (5 mg/kg KG) in den Wochen 0, 2 und 6 und danach alle 6 Wochen bis Woche 96. Röntgenaufnahmen der lateralen Hals- und Lendenwirbelsäule wurden bei Baseline und in Woche 102 angefertigt und unter Verwendung des „Modified Stoke Ankylosing Spondylitis Spine Scores" (mSASSS; 0–72) ausgewertet. Die radiographischen Veränderungen der Patienten der ASSERT-Infliximab-Gruppe wurden mit denen von Patienten der „Outcome in AS International Study" (OASIS)- Kohorte verglichen, einer Patientenpopulation, die nach einem festgelegten Protokoll beobachtet wurde und keine Anti-TNF-Therapie erhielt. Die Röntgenaufnahmen beider Patientenkohorten wurden digitalisiert und der Ursprung der Filme verblindet. Die Filme wurden von zwei Auswertern gelesen, wobei die zeitliche Abfolge der Aufnahmen nicht bekannt war. Als primärer Endpunkt wurde die mittlere Veränderung des mSASSS im Zeitraum zwischen Baseline und 2 Jahren gewählt. Der Unterschied zwischen den zwei Gruppen wurde mittels Kovarianzanalyse der Van-der-Waerden-normalisierten Progressionsscores mit Baseline mSASSS als Kovariate untersucht.

Resultate: Zwischen der ASSERT-Infliximab-Kohorte und der gesamten OASIS-Kohorte konnte kein statistisch signifikanter Unterschied bei der Veränderung des mSASSS von Baseline bis Woche 102 gezeigt werden (**Tabelle 2**). Die Ergebnisse waren ähnlich, wenn die ASSERT-Infliximab-Kohorte mit Patienten der OASIS-Kohorte verglichen wurde, welche die Auswahlkriterien der ASSERT-Studie erfüllten (OASIS angepaßt). Zusätzliche Sensitivitätsanalysen und Anpassungen bezüglich des Gebrauchs von NSAR beeinflußten die Resultate nicht.

Schlußfolgerung: Im Vergleich mit einer historischen Datenbank zeigte die Therapie mit Infliximab über 2 Jahre bei Patienten mit Spondylitis ankylosans in der ASSERT-Studie keine Hemmung der radiographischen Progression, gemessen als Veränderung des mSASSS.

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Remission of rheumatoid arthritis after treatment with ^{90}Yttrium ibritumomab tiuxetan (Zevalin®)

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Purpose: The therapy of patients with rheumatoid arthritis (RA) and coexisting malignancy is a challenge since many of the most potent treatments, e. g. tumor necrosis factor α (TNFα) blockers are contraindicated.

Methods: We report a case of a 67-yr-old Caucasian female with a lymphocytic non-Hodgkins lymphoma and active seropositive RA treated with a ^{90}Yttrium-labelled anti-CD20 antibody (^{90}Y-ibritumomab tiuxetan-Zevalin®).

Results: A 67-yr-old Caucasian female was first diagnosed with seropositive RA in 1955. She was treated in chronological order with hydroxychloroquine, gold i. m. and methotrexate (MTX). In 1999 she was diagnosed with a B-cell non-Hodgkins lymphoma (B-NHL) and MTX was stopped. Subsequently she received prednisolone as monotherapy for both NHL and RA. In November 2006 she was admitted to the hospital because of an acute exacerbation of her RA with 14 tender and swollen joints. The disease activity score DAS28 was 7.5 and the clinical disease activity index (CDAI) was 51.1. She had an elevated ESR of 64 mm/h and a CRP of 38 (normal < 8mg/l). Because of her B-NHL (Ann-Arbor Stage IV with bone marrow infiltration) we decided to start the classical NHL treatment regime consisting of two infusions of 250 mg/m^2 of rituximab followed by administration of 0.4 mCi/kg ^{90}Y-ibritumomab tiuxetan as a single course. At day 0 the number of tender and swollen joints was 23 and 10, respectively. Her baseline DAS28 was 6.2

Tabelle 2: Braun J et al.

Δ mSASSS, BL-Woche 102	OASIS gesamt	OASIS angepaßt	ASSERT-Gruppe
N auswertbar (N gesamt)	165 (192)	61 (70)	156 (201)
Mittelwert ± SD	1,0 ± 3,2	1,2 ± 3,9	0,9 ± 2,6
Median (Interquartilbereich)	0,0 (0,0; 1,3)	0,0 (–0,2; 1,5)	0,0 (–0,5; 1,2)
Gesamtbereich	(–3,1; 25,7)	(–2,3; 25,7)	(–6,6; 12,2)
p vs. OASIS gesamt/angepaßt			0,541/0,683

and the CDAI was 33. Within 2 weeks after the application of the radioactive compound, the disease activity scores began to decrease (**Figure 2**). Three months after the infusion of ^{90}Y-ibritumomab a complete remission of her non-Hodgkins lymphoma as well as her rheumatoid arthritis was achieved.

Conclusion: In this case of concomitant B-NHL and active RA treatment with Y^{90}-ibritumomab tiuxetan was highly effective. The application of radioactive anti-CD20 antibodies for rheumatoid arthritis should be further considered.

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Sequential etanercept and rituximab therapy in patients with active RA – SERRA

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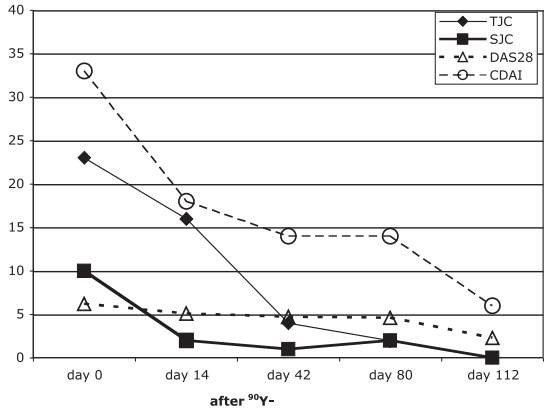
Objective: During the last few years the therapeutic options for the treatment of rheumatoid arthritis (RA) have improved dramatically. Anti-TNF-therapies now play a pivotal role in the treatment of RA patients. In additon, B-cell depletion therapies have also proven their efficacy. Unfortunately, there are still patients who do not show a satisfying respond to either of the treatments alone. Therefore it may be suggested that a depletion of B-cells by rituximab would be eligible to improve the efficacy of subsequent anti-TNF therapies. Still there are a lot of concerns about the increased risk of both bacterial (anti-TNF) and viral (B-cell depletion) infections as shown in combinations of anti-TNF and anti-IL1 therapies. Our pilot study was performed to test the safety of sequential B-cell depletion and anti-TNF therapies.

Methods: Four female patients with longstanding seropositive RA refractory to conventional DMARDS were included in the study. All received two courses of 1000 mg rituximab at day 1 and 15. Treatment with etanercept 2 x 25 mg/week was started at week 6. The patients were followed up for 28 weeks. Monthly visits were performed. Clinical efficacy was measured by the Disease Activity Score (DAS) 28. Serum and EDTA samples of all patients were collected at every visit for determination of CRP, ESR and B-lymphocyte counts.

Results: During the whole observation period no severe infections were observed. One patient delivered an unspecific bacterial infection of the upper respiratory tract at week 16 that could be managed easily by oral antibiotic treatment. A significant decrease in DAS28 and ESR could be achieved in all patients. The mean DAS28 decreased from 6.3 ± 0.77 at baseline to 3.0 ± 1.2 at week 28 (p = 0.003) and mean ESR levels decreased from 52.5 ± 15.0 to 20.5 ± 14.2 (p = 0.02). In three patients the B-lymphocyte counts decreased as expected by week 12 and did not reach normal levels during observation period. One patient already had a B-lymphocyte count below the normal limit and showed no significant change after therapy with rituximab, though clinical response was also given. No significant changes in RF-levels were observed.

Figure 2: Brezinschek HP et al.



Conclusion: The sequential treatment with rituximab and etanercept seems to provide a promising new therapy concept. In our observation no serious infections were developed. Furthermore, all patients showed a good clinical response that could be prolonged over the observation period.

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Value of real-time sonoelastography: comparison of findings between healthy volunteers and patients with symptomatic Achilles tendons

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Introduction: Rheumatoid diseases are frequently associated with Achilles tendinopathy: Although rheumatoid arthritis is considered a disease of joints, it can exhibit a variety of other musculoskeletal manifestations, such as the Achilles tendon. In ankylosing spondylitis Achilles tendinopathy often is the first symptom, and, Reiter's syndrome is another cause of Achilles tendon disorders. Psoriatic arthritis can occur with peripheral enthesitis, particularly Achilles tendinopathy. The purpose of this study was to assess Achilles tendons with sonoelastography (EUS), a new ultrasound method, and to compare it with conventional ultrasound (US) and magnetic resonance imaging (MRI). EUS can assess and illustrate elasticity properties of tissues and may differentiate pathological areas, where echogenicity and echotexture in US appear very similar to the surrounding healthy tissue.

Materials and Methods: 25 consecutive patients (14 female, 11 male; mean age 55 years; age range 44–66 years) and 25 healthy volunteers were examined with EUS and US. Ethics committee approval and informed written consent were obtained. Longitudinal and transversal images of proximal-, middle-, and distal third were performed. Twenty-two symptomatic Achilles tendons underwent MRI. Grading for US and MRI was: grade 1: normal tendon, grade 2: thickened, but homogeneous tendon, grade 3: inhomogeneous tendon with or without thickening. Grading for EUS was: grade 1: blue, green (hard tissue), grade 2:

yellow (soft tissue), grade 3: red (softest tissue).

Results: In healthy volunteers, 93.3 % of EUS images were graded as normal (grade 1). Patients showed grade 3 in the distal (64 %), middle (80 %), and proximal part (28 %) by EUS, showing good correlation with US and MRI (respectively P < .001). In asymptomatic contralateral tendon, we found an overall statistical significant difference (P < .001), located in the subanalysis in the middle third by using both US and EUS. By using EUS, statistical significant difference in detection of tendinopathy in the distal part (P < .001) was found. Interobserver variability was 2.9 %.

Conclusion: EUS detected sensitively alterations in symptomatic Achilles tendons correlating with MRI and US. EUS was more sensitive in detection of subclinical alterations in proximal and distal tendon parts, and contralateral Achilles tendons of patients when compared with US.

Preliminary results were accepted for oral presentation at the Congress of the Radiological Society of North America, Chicago 2006, under submission 2007.

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Ultrasound-guided sacroiliac joint injection: Definition of sonoanatomic landmarks validated by CT

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Introduction: Rheumatoid diseases, especially ankylosing spondylitis and psoriatic arthritis, are very common causes of sacroiliitis. Injection of intraarticular corticosteroids into the sacroiliac joint (SI joint) is considered as a useful additional therapeutic approach for sacroiliitis, besides physiotherapy and systemic medication. Clinically guided SI joint injections are a difficult procedure, because the SI joint can be challenging to enter with a needle due to its complex anatomy. Therefore image guidance seems to be a crucial issue to improve the intraarticular success rate of SI joint injections, and image guided needle placement using fluoroscopy, computed tomography (CT) or magnetic resonance imaging (MRI) have been advocated by several studies for precise needle placement. Only one study is available for ultrasound (US) guidance, however showing extraarticular placement in 23.3 %. The purpose of the study was to define sonoanatomic landmarks for successful intraarticular needle placement into SI joint and to assess the feasibility of US guided needle insertion for intraarticular injection of the SI joint at two different puncture levels.

Material and Methods: In 11 human cadavers (22 SI joints) US guided needle insertion was performed with a 2.5–6.0 MHz curved array transducer at two different puncture sites: upper level at the level of posterior sacral foramen one and lower level at the level of posterior sacral foramen two.

Results: CT confirmed correct intraarticular needle placement in 35/44 SI joints (79.5 %); upper level: 15/22 (68.1 %); lower level: 20/22 (90.9 %). CT guided needle repositioning was possible at the upper level in 3 SI joints (13.6 %), and at the lower level in 1 SI joint (4.5 %); overall needle placement was feasible in 39/44 SI joints (88.6 %). US guided needle insertion showed a significantly higher success rate for the lower level ($p < 0.05$).

Conclusion: US guidance for needle insertion into SI joint is feasible, when defined sonoanatomic landmarks are used, demonstrating a high success rate when performed at the lower level. Lack of radiation and real-time performance are the main advantages compared to conventional CT- and magnetic resonance imaging-guided injections.

Preliminary results were accepted at EULAR 2004, work in progress until 2006, final results as original paper under submission 2007.

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Infliximab, etanercept, and adalimumab switching in patients with rheumatoid arthritis in the Consortium Of Rheumatology Researchers Of North America (CORRONA) database

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Introduction: Previous studies have demonstrated that anti-tumor necrosis factor a (TNF) infliximab, adalimumab, and etanercept are effective therapies for patients with rheumatoid arthritis (RA). The availability of these TNF agents provides physicians with the flexibility of choosing a TNF for an individual patient and switching from one TNF agent to the other, which could benefit that individual patient. In this study we investigated the switching rate from one type of TNF to the other, in patients with RA.

Methods: We utilized the CORRONA database, which collects data from both rheumatologists and patients at the time of a clinical encounter. Data are collected as often as every 3 months in RA. Patients enrolled between March 2002 and February 2006 were included in this analysis. Patients were excluded from this analysis if they received any TNF prior to being enrolled in CORRONA. Initial TNF status was defined at the first visit for a patient in the database, and last TNF status was defined as the drug received at the time of the last clinical encounter. The study population was comprised of patients who were prescribed any TNF agent while in the database and stayed in CORRONA for at least 6 months on a TNF agent. If a patient was receiving a TNF agent at enrolment and was switched to another TNF drug while in the database, this patient was counted as a switch in this study.

Results: 10,434 patients with RA were identified in CORRONA; 2,390 (23 %) patients met the study criteria. Out of those, 46 % started on infliximab, and 54 % on other TNFs (etanercept, or adalimumab). Of the patients starting on infliximab, 85 % remained on infliximab compared to 76 % of patients starting and ending on other TNFs ($p < 0.0001$) during the study period. Among the 1,100 patients who started on infliximab, 78 (7.1 %) patients switched to other TNFs. Of the 1,290 patients who started on other TNFs 52 (4.0 %) patients switched to infliximab, and 67 (5.2 %) patients switched within the other TNF agents. Patients who switched from infliximab were younger, more likely to be females, less educated, and less likely to have private insurance, compared to other TNFs switchers. The mean time to the first switch took longer for infliximab, 722 days, than for other anti-TNF agents, 648 days (P = 0.025) in the CORRONA registry.

Conclusion: Our study demonstrates that switching between TNF therapies occurs. Patients treated with infliximab remained on the therapy more than those treated with other TNF agents. The duration of therapy prior to switching was longer for infliximab than for other TNF agents (P = 0.025). The clinical importance of these findings will require further follow-up.

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Persistency among anti-tumor necrosis factors in the treatment of rheumatoid arthritis from a payor perspective

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Introduction: Anti-TNF therapies (infliximab [IFX], etanercept [ETA], adalimumab [ADA]) are effective for the treatment of RA patients. The aim of the present study was to evaluate persistence of anti-TNF therapy utilizing the Wolters Kluwer (WK) and PharMetrics claims databases.

Methods: Longitudinal claims data from PharMetrics and WK was conducted. Patients enrolled in the same plan for 12 months following the initial claim were evaluated. The first anti-TNF encounter (index date) among RA patients in the period Dec 1, 2003–Feb 28, 2004 was identified. Only patients in the PharMetrics database continuous plan eligible for at least 12 months following the initial claim were evaluated. Three mutually exclusive cohorts were developed based on their index biologic: IFX, ETA and ADA. Anti-TNF persistence (%) was defined as the % of patients in each cohort that either (A) had an anti-TNF claim in the calendar month 12 months after the index date, (B) had days supply from a prior claim that carried through to the calendar month 12 months after the index date or (C) in the case of IFX, had a claim within 56 days of the calendar month 12 months after the index date. Beginning with the Feb 2004 cohort, the PharMetrics-derived persistency rates were updated based on a trend analysis of WK claims data for index dates of Feb 2004, March 2005, and Sept 2005.

Results: 6,481 patients (2,057 IFX; 3,534 ETA; 890 ADA) were analyzed. In the Feb 2004 cohort, the IFX cohort was significantly more persistent (76 % vs ETA 72 % and ADA 68 %, p < 0.05). Based on a trend analysis of WK data cohorts initiating on Feb 2004, March 2005, and Sept 2005, the difference between IFX and other anti-TNFs appears to be at least as great and is currently estimated at 76 % IFX, 70 % ETA and 66 % ADA (**Figure 3**).

Conclusion: IFX patients are more persistent with anti-TNF therapy vs patients on other anti-TNF therapies. Further studies need to evaluate the impact of persistence on clinical outcomes.

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Comparison of therapeutic persistence among anti-tumor necrosis factors in the treatment of rheumatoid arthritis

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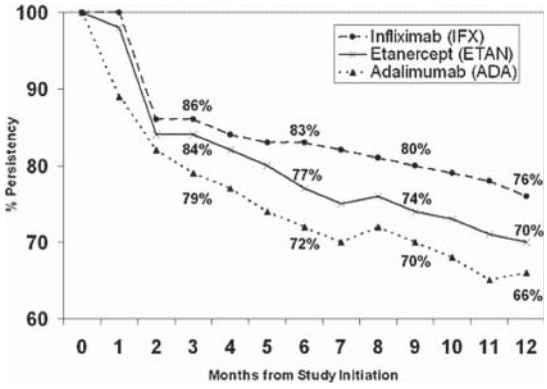
Introduction: The aim of the present study was to evaluate persistence of anti-TNF treatment among patients with rheumatoid arthritis (RA) utilizing a managed care database.

Methods: A retrospective study utilizing the US PharMetrics managed care claims database was conducted. The first anti-TNF (infliximab, etanercept or adalimumab) encounter (index date) among RA patients between January 1, 2001 and January 1, 2004 was identified. Patients were required to have a minimum of 12-months of continuous plan eligibility prior to and following their index biologic date. Three mutually exclusive cohorts were developed based on their index biologic; infliximab plus methotrexate (MTX); etanercept plus MTX; and adalimumab plus MTX. Anti-TNF persistence (%) was defined as the number of days between first biologic prescription and their last biologic encounter, divided by 365 and multiplied by 100. Both univariate and multivariate analyses were applied to determine if differences in persistence existed between the three cohorts.

Results: A total of 1,242 patients were analyzed consisting of 490 (39.4 %) infliximab plus MTX; 607 (48.9 %) etanercept plus MTX; and 145 (11.7 %) adalimumab plus MTX. Over two-thirds of the patients were female and the mean age was 50.0 years. The Charlson co-morbidity index and disease staging were consistent among the three cohorts. The infliximab plus MTX cohort was more persistent (78.0 % than the other 2 cohorts – etanercept plus MTX 73.6 % and adalimumab plus MTX 70.8 %) and was statistically significant (p < 0.05). After adjusting for potential confounding variables (age, gender, Charlson co-morbidity index and disease severity), infliximab patients had 5.4 % more persistence than etanercept (P < 0.01), and 7.0 % more than the adalimumab group (P < 0.05). Etanercept patients were more persistent than the adalimumab group, however, the difference was not significant (P > 0.05).

Conclusion: These results indicate that patients on infliximab plus MTX are more persistent with anti-TNF therapy, compared to

Figure 3: Dabbous O et al. Persistency of anti-TNF therapy in RA patients (september 2006)



other anti-TNFs. Further studies are needed to evaluate the impact of persistence on clinical outcomes.

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Comparison of switching patterns among anti-tumor necrosis factors in the treatment of rheumatoid arthritis

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Introduction: The aim of the present study was to evaluate switching patterns among anti-TNFs in patients with rheumatoid arthritis (RA).

Methods: A retrospective study utilizing the US PharMetrics managed-care claims database was conducted. The first anti-TNF encounter among RA patients between January 1, 2001 and January 1, 2004 was identified. Patients were required to have a minimum of 12 months of continuous plan eligibility prior to and following their index date. Three mutually exclusive cohorts were developed based on their index biologic (infliximab, etanercept and adalimumab) plus methotrexate (MTX). The rates of switching and time before switching were examined. Descriptive and chi-square statistical analyses were conducted to determine if differences existed among the three cohorts.

Results: A total of 1,242 patients were analyzed consisting of 490 (39.4 %) infliximab plus MTX; 607 (48.9 %) etanercept plus MTX; and 145 (11.7 %) adalimumab plus MTX. Over two-thirds of the patients were female and the mean age was 50.0 years. The Charlson co-morbidity index and disease staging were similar among the three cohorts. During the 12 months follow-up, 39 patients (7.9 %) in the infliximab plus MTX cohort switched compared to 72 patients (11.9 %) in the etanercept group and 23 patients (15.9 %) in the adalimumab group. Chi-square analyses indicated the differences were statistically significant ($p < 0.05$) as compared to the infliximab plus MTX cohort. The infliximab group had an average time of 195.9 days before switching, compared to 183.1 days in the etanercept group, and 165.3 in the adalimumab group, but this was not statistically significant.

Conclusion: The rate of switching and time before switching are important measures of the effectiveness of RA treatment in real world practice. This study found that infliximab plus MTX is associated with a longer time before switching and a significantly lower switching rate, as compared to the other anti-TNFs. Further studies are needed to evaluate the impact of switching on clinical and economic outcomes.

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Erfolgs- und Komplikationsrate der perkutanen Vertebroplastie (PVP) bei Patienten mit Osteoporose

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Einleitung: Die perkutane Vertebroplastie (PVP) ist ein evidenzbasiertes, minimalinvasives Verfahren zur Therapie der Wirbelsäulendeformation und assoziierter Schmerzen nach vertebraler Kompressionsfraktur (VCF) bei Patienten mit OP [1, 2]. Zielsetzung dieser Analyse war die Evaluierung der technischen Erfolgs- und Komplikationsrate bei Patienten mit PVP nach VCF.

Materialien und Methoden: Die Datenerfassung erfolgte retrospektiv durch Auswertung der Krankengeschichten und Interventionsprotokolle. Die PVP wurde von zwei Interventionisten durchgeführt (F. K., P. B.). Die CT-/Fluoroskopie-gezielte PVP mit zusätzlicher Führung durch den konventionellen C-Arm wurde zwischen Oktober 2003 und Februar 2007 wie anderweitig beschrieben [3, 4] durchgeführt.

Resultate: Eine Gesamtanzahl von n = 133 (TH4–L5) Interventionen wurde analysiert. Die PVP wurde bei n = 85 Patienten durchgeführt (1 w/14 m, mittleres Alter 75,5 ± 9,5 a [53–93a]).

Eine postinterventionelle Zementleckage wurde bei 44/85 Patienten (51,7 %) oder bei 50/133 Wirbeln (37,6 %) gefunden. Die Position der Leckage verteilte sich wie folgt: 9,7 % (n = 13) in basivertebrale Venen, 5 % (n = 7) in paravertebrale Strukturen einschließlich paravertebraler Venen, 15 % (n = 20) in angrenzende Disci (obere oder untere Endplatte) und 7 % (n = 10) zum epiduralen venösen System.

Alle PVPs wurden unter Lokalanästhesie und Sedierung durchgeführt. Es traten keine klinisch relevanten neurologischen oder embolischen Komplikationen auf. Es gab keine verfahrensbezogene Mortalität.

Schlußfolgerung: Die PVP kann bei Patienten mit OP und VCF sicher und effektiv durchgeführt werden. Eine Zementleckage wird durch Kombination von CT und herkömmlicher Fluoroskopie häufig dargestellt, wobei in der analysierten Patientengruppe klinisch relevante neurologische und/oder embolische Komplikationen vermieden werden konnten.

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DAS28 values differ considerably depending on patient's pain perception and gender

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Objective: To analyze, whether the disease activity index including a 28 joint count (DAS28) is equally applicable for the total rheumatoid arthritis (RA) population.

Patients and Methods: 557 RA out-patients (432 female/125 male), median age 64 years (18–85), median disease duration 48 months (2–548) were enrolled consecutively into this cross sectional study. The DAS28 and additionally, physician's global assessment of disease activity (PhGA), patient's assessment of pain (VASpain), C-reactive protein (CRP; mg/dl), rheumatoid factor (RF) and disease duration were recorded. For all comparisons of DAS28 values t-tests were applied. Moreover, linear regression analy-

sis was performed for each possibly confounding factor.

Results: The mean DAS28 in female patients was 3.66 (± 0,57 SEM), while 3.01 (± 1,12 SEM) in males, p < .000. DAS values in patients with early RA (< 37 months) were significantly higher than in patients with advanced RA (3.62 [± 0,67 SEM] vs 3.37 [± 0,81 SEM]; p < .017). Regression analysis revealed a highly significant relationship between DAS28 levels and patient's pain rating (r = .592; p < .0001). Pain was seen to exert the far highest influence on the DAS28 (p < .0001), while of the other factors only age was also significantly correlated with DAS28 values (p < .008 for females and p < .007 for males).

Conclusion: The DAS28 values differ considerably depending primarily on the patient's pain perception and gender and to a lesser degree on patient's age, whereas disease duration and RF were found indecisive.

Reference:
DAS28 values differ considerably depending on patient's pain perception and gender. J Rheumatol 2007, in press.

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THE RADAI-5 IS A RELIABLE TOOL FOR DISEASE ACTIVITY ASSESSEMENT IN RHEUMATOID ARTHRITIS PATIENTS

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Objective: Some exclusively patient self-assessment questionnaires, such as the modified Health Assessment Questionnaire (M-HAQ), the Rheumatoid Arthritis Disease Activity Index (RADAI) or the Rapid Assessment of Disease Activity in Rheumatology questionnaire (RADAR) have been proposed for RA activity monitoring.

Although it would give an advantage particularly with respect to time, if the patient performs disease activity assessment himself by completing a questionnaire during the waiting-time, none of the patient administered indexes, except the HAQ, is widely used in daily routine. An easy to evaluate instrument would of course constitute the main prerequisite.

We attempted to evaluate the psychometric properties and external validity of a modified version of the Rheumatoid Arthritis Disease Activity Index (RADAI), a patient administered assessment tool.

Patients and Methods: 169 rheumatoid arthritis (RA) out-patients were enrolled into this study. Patients were asked to complete the RADAI and the modified RADAI-5. The modified RADAI-5 comprises the four questions of the original RADAI, question 5 concerning the self assessment of the tender joints was omited. One question about the general health was added. The RADAI-5 was established in German language and has a Likert format from 0 to 10. Additionally, all core-set parameters to be enabled to calculate the DAS28-ESR, the DAS28-CRP, the SDAI and the CDAI were assessed as well as patient's pain (on a visual analogue scale [VASpain] 0–100). Internal consistency testing was performed by calculating Cronbach's alpha. To test for absolute agreement between the disease activity scales the average measure intra-class correlation coefficient was calculated. In order to double-check convergent validity Spearman's rho for the RADAI-5 and the core set measures was determined.

Results: The mean values for the RADAI and the RADAI-5 were 2.9 (0.0–9.27) and 3.07 (0.0–10.0) respectively. The other mean values were as follows: DAS28-ESR 3.51 (0.28–6.67), DAS28-CRP 3.19 (1.12–5.83), CDAI 11.53 (0.0–44.6), SDAI 12.36 (0.1–44.9). So the patient group can be regarded moderate actively diseased. Cronbach's alpha was found the highest for the RADAI-5 (0.913) and the lowest for the DAS28-CRP (0.510), for DAS28-ESR 0,553. After having proven internal consistency of the new index, the degree of congruence between the established and validated disease activity indexes and the RADAI-5 had to be investigated. To this end the Spearman rank correlation coefficient was calculated. Agreement analysis revealed a highly significant correlation (all p's < .0001) of the RADAI-5 with all other comparator instruments. The RADAI-5 also proved to be significantly correlated with the SJC and TJC as well as with physician's assessment of disease activity, a borderline significance could be established with CRP-levels, however not with the ESR.

Conclusion: It could be demonstrated, that a modified version of the RADAI, refraining from joint counts, is capable of measuring RA activity. The reliability and convergent validity of this RADAI-5 could be proven. The internal consistency of the patient administered questionnaires appeared to be substantially higher than the one of the composite indexes.

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DIE GENERATION 60+ IN 7 RHEUMAAMBULANZEN IN ÖSTERREICH

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Einleitung: Rheumatische Erkrankungen treten gehäuft im höheren Lebensalter auf. Daraus läßt sich vermuten, daß ein großer Anteil der Patienten in Rheumaambulanzen der Generation 60+ angehört.

Methode: Mittels Fragebogen wurden in 7 Rheumaambulanzen Österreichs, von denen 6 von Additivfachärzten für Rheumatologie betreut werden, Daten von Patienten mit 60 Jahren oder älter erhoben, die innerhalb von 4 Wochen im Zeitraum zwischen Juni und September 2007 behandelt wurden.

Ergebnisse: Von den insgesamt behandelten 1421 Patienten gehörten 556 (39,1%) der Generation 60+ an. Davon hatten 439 Patienten (78,9 %) die Diagnose einer entzündlich rheumatischen Erkrankung. Für 113 Patienten (20,3 %) war es der erste Besuch in der jeweiligen Rheumaambulanz, für alle anderen Patienten waren die Besuche geplante Kontrolluntersuchungen. Eine Aufgliederung in Altersgruppen in 10-Jahres-Intervallen war für 375 Patienten (Daten von 6 Ambulanzen) der Generation 60+ möglich:

- 60–69a: 221 Patienten (58,9 %), davon 50 Erstbesuche und 163 (73,8 %) Diagnosen einer entzündlich rheumatischen Erkrankung
- 70–79a: 129 Patienten (34,4 %), davon 56 Erstbesuche und 98 (76,0 %) Diagnosen einer entzündlich rheumatischen Erkrankung
- 80–89a: 25 Patienten (6,6 %), davon 7 Erstbesuche und 15 (60 %) Diagnosen einer entzündlich rheumatischen Erkrankung

Diskussion: Entgegen der starken Zunahme rheumatischer Erkrankungen im Alter ist der Anteil der Generation 60+ in den befragten Ambulanzen knapp unter 40 % und nimmt mit steigendem Lebensalter rapide ab. Die falsche Annahme, daß rheumatische Beschwerden zum Alterungsprozeß gehören

und nicht behandelbar sind, könnte dafür eine mögliche Ursache sein. Es erscheint dringend notwendig, in der Generation 60+ Bewußtsein dafür zu schaffen, daß eine fachkompetente rheumatologische Abklärung und Therapie bis ins hohe Lebensalter gerechtfertigt und sinnvoll ist.

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Patient's pain perception and gender highly influence SDAI and CDAI-levels in rheumatoid arthritis patients

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Objective: To get insights, whether the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) are equally applicable for the total rheumatoid arthritis (RA) population.

Patients and Methods: 557 RA out-patients (432 f/125 m; median age 64 yrs [18–85], median disease duration 48 months [2–548]) were enrolled consecutively into this cross sectional study. The SDAI, the CDAI, the DAS28 and additionally, patient's assessment of pain (visual analogue scale [VASpain] 0 to 100), rheumatoid factor and disease duration were recorded. Internal consistency analysis by calculating standardized item alpha and agreement analysis by the intraclass correlation (ICC) for the SDAI and CDAI levels were performed. For all comparisons of SDAI and CDAI values nonparametric tests were applied. Moreover linear regression analysis was performed for each probably confounding factor.

Results: The median SDAI and CDAI in female patients were 12.2 (0.7–46.6) and 11.3 (0.0–42.1) respectively, while they amounted to 7.98 (0.1–35.2) and 7.05 (0.0–32.0) in males, ($p < .000$) alpha amounted to 0.706 for the SDAI, and to 0.749 for the CDAI, the ICC was 0.989. SDAI and CDAI values in patients with early RA (< 37 months) were insignificant different to the respective ones in patients with advanced RA (SDAI: 11.0 vs. 11.8; CDAI: 10.2 vs. 10.9). Regression analysis revealed a highly significant relationship between the SDAI and CDAI levels and patient's pain rating ($r = .666$ for the SDAI; $p < .000$; $r = .671$ for the CDAI; $p < .000$). On multiple regression analysis pain was seen to exert a highly significant influence on the SDAI and CDAI-levels ($p < .000$), while the other factors, namely age, disease duration and rheumatoid factor were found unrelated to SDAI and CDAI values irrespective of analysed in females and males separately or the whole patient's population. The DAS28, in contrast, was fould also dependent upon patient's age to a significant degree.

Conclusion: The SDAI and CDAI values differ considerably depending primarily on the patient's pain perception and on gender. Patient's age, disease duration and RF were found indecisive for the values of the respective disease activity indexes.

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Does methotrexate treatment impair the response to vaccinations in patients with rheumatic diseases?

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Background: Rheumatoid patients are at increased risk of developing infectious diseases, not only because of the disease itself but also due to the immunosuppressive therapy. Therefore vaccination should be recommended to rheumatoid patients, although methotrexate medication could impair the responsiveness to vaccines.

Methods: PubMed search through July 2007 with emphasis on relevant studies about the immune response to various vaccines in patients with rheumatoid arthritis, systemic lupus erythematosus and other rheumatic diseases receiving methotrexate medication.

Results: 12 studies relating to vaccination in MTX-treated patients were found. The usage of methotrexate was not associated with decreased responsiveness to influenza vaccination in all studies, but the use of certain TNF-α-blockers (etanercept, infliximab) in combination with MTX showed controversial results with significant lower response rates in one study and no influence on response in another. Hepatitis B vaccination in patients with methotrexate treatment did not reduce the response. The results for pneumococcal vaccination in MTX patients were also controversial with no indicated influence on responsiveness in only one study and significant association with lower response rates in four studies. Furthermore, the combination of certain TNF-α-blockers (adalimumab) and MTX was associated with poor response, whereas the combination with other TNF-α-blockers (etanercept or infliximab) showed no significant impairments.

Conclusion: In none of the studies clinical or laboratory worsening of disease activity was observed. Neither of them showed any increase of autoantibody levels. Still, further studies with influenza and pneumococcal vaccines will be necessary to analyse the differences of concomitant treatment with various TNF-α-blockers in MTX-patients. In addition, the effect of high MTX dosages on response rates and hypothesized boosting effects on antibody levels in MTX-patients being vaccinated has to be determined.

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Characteristics of Austrian patients initiated on TNF blocker therapy in 2006

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Background: Points to consider, regarded patient relevant were identified by experts' consensus applying the Delphi technique. Subsequently, also the parameters' thresholds with respect to the initiation of a TNF-α blocker were identified by voting and calculating the lower 95 % CI for the experts' opinion's mean [1].

Objective: After having done so the group agreed to retrospectively assess all its patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) started on a TNF-α blocker in 2006 with respect to the parameters and the respective elaborated thresholds.

Methods: It was possible to assess 650 patients initiated on a TNF blocker retrospectively: RA: n = 408, (53,26a; 340f, 68m); PsA: n = 93,(48,90a; 34f, 59m) AS: n = 149, (42,22a; 41f, 108m). It can be assumed that this number represents about 25 % of all Austrian patients who started TNF blocking therapy in 2006. Patients were analyzed according to the parameters elaborated previously. The number of patients not meeting the thresholds regarded relevant were calculated. Moreover, the degree of documentation of each single parameter was registered.

Results: **Table 3** gives the means and the lower 95 % CI as the thresholds for the respective parameters in relation to the initiation of TNF blocker therapy in AS, PsA, and RA patients as expressed by the experts and the values identified retrospectively. The degree of documentation for the single parameters varied between 32 % (radiological progression in PsA patients) and 91.2 % (ESR in RA patients).

Conclusion: The parameters' means retrospectively identified for 2006 were on average lower than the respective mean values at the beginning of most clinical trials.The respective ranges indicate, that, at least in part, TNF blockers are initiated in patients at considerably low disease activity.

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The Polymyalgia Rheumatica Activity Score (PMR-AS) in daily use. Proposal for a definition of remission

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Objective: To confirm the reliability and applicability of the Polymyalgia Rheumatica Disease Activity Score (PMR-AS), and to establish a threshold for remission.

Methods: First, 78 patients with PMR (50 women/28 men, mean age 65.97 years) were enrolled in a cross-sectional evaluation. The PMR-AS, patient's satisfaction with disease status (PATSAT; range 1–5), erythrocyte sedimentation rate (ESR; first hour), and a visual analog scale of patients' general health assessment (VAS patient global; range 0–100) were recorded. Subsequently, another 39 PMR patients (24 women/15 men, mean age 68.12 years) were followed longitudinally. Relationships between the PMR-AS, PATSAT, ESR, and VAS patient global were analyzed by the Kruskal-Wallis test, Spearman's rank correlation, and kappa statistics. PMR-AS values in patients with a PATSAT score of 1 and a VAS patient global < 10 formed the basis to establish a remission threshold.

Results: PMR-AS values were significantly related to PATSAT ($P < 0.001$), VAS patient global ($P < 0.001$), and ESR ($P < 0.01$). PATSAT and VAS patient global were reasonably different (kappa = 0.226). The median PMR-AS score in patients with PATSAT score 1 and VAS patient global < 10 was 0.7 (range 0–3.3), and the respective 75th percentile was 1.3 to enhance applicability, a range from 0 to 1.5 was proposed to define remission in PMR. The median ESR in these patients was 10 mm/hour (range 3–28), indicating external validity.

Table 3: Leeb BF et al.

Parameter AS	**Expert's mean**	**Lower 95 % CI**	**Patients initiated 2006 (n = 149) mean**	**Range**
BASDAI	3.6	3.4	5.98	2.63–9.61
NSAID failure	2	2	2.26	1–5
Peripheral arthritis	1	1	1.63	0–16
Positive radiology, incl. MRI	yes	yes	yes in 90 % of the pts.	yes–no
Parameter PsA	**Expert's mean**	**Lower 95 % CI**	**Patients initiated 2006 (n = 93) mean**	**Range**
SJC + Dact. + Enth.	1	1	5.1	0–22
TJC + Dact. + Enth.	3	2	8.6	0–36
Skin involvement (phys. ass.; 0–10)	0.3	0	4	0–10
DMARDs failures	1	1	1.83	0–5
Radiol. progression	no	no	51 % of the pts.	no–yes
Spine involvement	no	no	26.9 % of the pts.	no–yes
Parameter RA	**Expert's mean**	**Lower 95 % CI**	**Patients initiated 2006 (n = 408) mean**	**Range**
SJC	1	1	7.03	0–32
TJC	4	2	9.64	0–49
VAS GH	43	35	47.61	0–100
CRP (mg/dl; -0,5 normal)	0.7	0.5	1.85	0–13.2
ESR (1st hour)	15	11	35.41	2–113
N DMARD failure	2	1	2.47	0–8
DAS28 (calculated)		3.24	5.02	0.77–8.09

Conclusion: We demonstrated the reliability, validity, and applicability of the PMR-AS in daily routine. Moreover, we proposed a remission threshold (0–1.5) founded on patient-dependent parameters.

Reference:
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Treatment with corticosteroids improves augmentation index in patients with polymyalgia rheumatica

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Background: Arterial stiffness is a marker of vascular dysfunction [1] and is associated with a number of traditional cardiovascular risk factors. There is growing evidence that inflammation plays a major role in the initiation and progression of atherosclerosis [2]. Pulse wave analysis (PWA) allows non-invasive evaluation of the augmentation index (AIx), a surrogate marker of arterial stiffness, and of central aortic pressure by applanation tonometry of the radial artery [3].

Objectives: Because PMR is known to respond well clinically to corticosteroids, we wanted to examine whether this treatment might also have a beneficial effect on arterial stiffness in these patients. The aim of this study thus was to investigate the influence of therapy with steroids on AIx in patients with newly diagnosed PMR.

Methods: Included in the study were 13 patients with newly diagnosed PMR, who had not been previously treated with corticosteroids. All subjects fulfilled the Bird criteria [4]. PWA was performed using radial applanation-tonometry with a high-fidelity micro-manometer (SPC-301, Millar Instruments) and the Sphygmocor apparatus (Sphygmocor AtCor Medical, version 6.31). Thereby, AIx and the subendocardial viability ration (SEVR), a measure of myocardial perfusion relative to cardiac workload [3], as well as central aortic pulse pressure can be measured. PWA was performed before and 4 weeks after initiation of treatment with 25 mg prednisolone daily as a single morning dose. To exclude the influence of heart-rate on the AIx, the standardized value for 75 beats per minute is given [5]. In addition, we analysed markers of systemic inflammation (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen).

Results: After treatment with corticosteroids ESR (62.6 ± 24.4 vs 13.7 ± 11.4 mm/h), CRP (7.1 ± 5.5 vs 0.6 ± 0.9 mg/dl) and fibrinogen (700.8 ± 193.3 vs 332.7 ± 84.7 mg/dl) all improved statistically significant ($p < 0.001$ for all). AIx was reduced from 28.5 ± 9.1 to 25.3 ± 9.9 ($p = 0.006$). SEVR improved from 130.2 ± 17.1 % to 155.3 ± 31.7 % ($p = 0.011$). There was no statistically significant difference in brachial or central systolic and diastolic blood pressure before versus after treatment ($p > 0.05$).

Conclusion: The results of this study indicate that treatment with corticosteroids reduces AIx, a marker of arterial stiffness, in patients with newly diagnosed PMR.

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Does a relationship between personality and rheumatoid arthritis exist?

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Objective: Aim of this study was to investigate, whether the personalities of rheumatoid arthritics (RA) differ from those of non-rheumatologic patients.

Patients and Methods: For the purpose of this study the authors designed a psychological questionnaire. A total of 226 patients (113 RA patients and 113 control persons [CO]) were asked to fill in this questionnaire assessing their psychological profile as well as demographic data on their family history. The control group consisted of healthy controls as well as scarcely affected individuals as well as chronically ill patients.

Results: The questionnaire was completed without any problems by 98 % of patients. No statistical difference in any of the 26 questions was to be observed. Only the question concerning sibship revealed a trend towards single childhood in the RA group ($p = 0.07$).

Conclusion: There was no difference in the psychological profile of RA and CO detectable. The most remarkable result was the higher prevalence of single children in the RA group, although this difference did not reach statistical significance. This topic is worth being addressed in a larger cohort of patients.

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Is the SF-SACRAH able to screen a nephrologic patient cohort for hand disorders?

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Purpose: The SF-SACRAH is a score for the assessment of rheumatologic hand disorders and has already been applied and validated in patients suffering from hand osteoarthritis (HOA) and rheumatoid arthritis (RA). Aim of this study was to test its capability as a screening instrument for rheumatologic and other hand affections in a primarily non-rheumatologic patient cohort.

Methods: Between November and December 2006 a total of 182 patients (104 renal transplant recipients [RTR], 78 hemo- or peritoneal dialysis patients [DP]) filled in the questionnaire. Mean age of the overall patient cohort was 55.3 years (DP: 60.3, RTR: 52 years), 78 were female, 104 male.

The mean SF-SACRAH value in an earlier study of 247 RA and HOA patients was 2.1. This value was taken as an arbitrary cut-off. A score exceeding 2.1 should identify patients with hand disorders. Subsequently all patients were clinically examined and divided into rheumatologically asymptomatic patients (ASY), patients with HOA or RA, and patients with other disabling conditions of the hands (MISC).

Results: According to the clinical examination 101 (55 %) patients were assigned ASY, 65 (36 %) patients showed a rheumatologic

hand disorder (63 HOA and 2 RA). In 16 (9 %) patients MISC (Dupuytren contracture, Carpal tunnel syndrome etc) were found. Total SF-SACRAH amounted to 0.6 (1.6) (median [IQR]). While there was no significant difference between the SF-SACRAH in ASY (0.8 [1.2] and HOA patients (1.3 [2.5]), it differed significantly between ASY and RA patients (3.8 [2.8]); (p = 0.04 Mann-Whitney U test). With the chosen cut-off of 2.1, the sensitivity of the SF-SACRAH to predict rheumatic hand disorders was 0.44. When adding MISC patients, it amounted to 0.52. The specificity for the respective cohorts of patients was 0.89. The positive predictive value of the SF-SACRAH amounted to 0.72 for rheumatic patients, when adding MISC patients it increased to 0.8. The respective figures for the negative predictive value were 0.71 and 0.69.

Conclusion: The SF-SACRAH proved its capability as a screening tool for rheumatic hand disorders in a primarily non-rheumatologic patient cohort for the first time. This study revealed a number of persons affected with different disorders of the hand. Therefore the potential use of the SF-SACRAH to screen other non-rheumatologic patient cohorts is worth being considered.

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Rheumatologische Ausbildung in der Lehrpraxis – ein Modell für die Zukunft?

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Einleitung: Derzeit ist die Absolvierung des Hauptfaches zur Erlangung des Zusatzfaches Rheumatologie nur an einer stationären rheumatologischen Einrichtung möglich, wohingegen die notwendigen Gegenfächer (Orthopädie, Radiologie und physikalische Medizin) auch im niedergelassenen Bereich absolvierbar sind. Angeregt durch die Erfahrungen in der internistischen Lehrpraxis erhob sich für die Autoren die Frage, ob die Ausbildungsvoraussetzungen im Setting einer Lehrpraxis auch für die Rheumatologie zu erfüllen wären.

Patienten und Methoden: Im Zeitraum von 05.02.2007–30.09.2007 hat die Autorin in einer rheumatologisch und gastroenterologisch spezialisierten Kassenordination ihre Facharztausbildung zur Internistin als Lehrpraxis komplettiert. Rheumatologiespezifische Laborbefunde wurden im angeschlossenen Labor erhoben. Die Autorin führte Gelenkspunktionen sowie intraartikuläre, intramuskuläre und paravertebrale Infiltrationen durch. Einmal wöchentlich fand in Kooperation mit einem Rheumaorthopäden eine Rheumasprechstunde mit Begutachtung interdisziplinärer Patienten statt. Die Therapie mit Biologika ist in dieser Ordination usuell und inkludierte Infusionen, s.c.-Therapien und die Anwendung von Biologika der 2. Generation. Als Vergleichsgröße wurde die ebenso lange Tätigkeit der Autorin in einer spezialisierten Rheumaambulanz eines österreichischen Krankenhauses herangezogen.

Ergebnis: Im angegebenen Zeitraum wurden von ihr 448 Patienten (29 %) erstuntersucht (Kontrollen eingerechnet, ca. 1550 Patientenkontakte), davon 331 Frauen (74 %) und 116 Männer (26 %), 49 % entzündlich-rheumatische, 20 % Osteoarthrosepatienten, 23 % mit anderen Gelenksaffektionen und 8 % allgemein-internistische Patienten. In einem vergleichbaren Zeitraum ergaben sich in der Ambulanz insgesamt ca. 1390 Patientenkontakte, davon 347 Erstbegutachtungen (25 %). Die für das Zusatzfach erforderliche Frequenz an Patientenkontakten bzw. praktischen Techniken erwies sich somit im Vergleich als ausreichend erfüllt. Es ist zu postulieren, daß Rheumatologie ein Fach ist, zu dessen Durchdringung Nachtdienste nicht zwingend notwendig sind, sondern vielmehr eine möglichst breite klinische Erfahrung gefordert wird.

Konklusion: Die Absolvierung des Zusatzfaches Rheumatologie oder zumindest eines Teiles davon wäre nach unseren Erfahrungen auch in der Lehrpraxis möglich. Voraussetzungen dafür sind entsprechende Patientenzahlen, die intensive Betreuung durch den Lehrpraxisinhaber mit der kontinuierlichen Möglichkeit einer Second Opinion sowie rheumatologische Vorkenntnisse des Lehrpraktikanten.

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Three rheumatoid arthritis disease activity scores in clinical routine

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Objective: To evaluate whether the disease activity cut-off values for the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) are in congruence with the EULAR response criteria (EULARC).

Patients and Methods: 570 rheumatoid arthritis (RA) out-patients were assessed and categorized according to the DAS28 (Disease Activity Score including a 28 joint count), the SDAI and the CDAI. The results were compared to the respective EULARC. Statistical evaluation was carried out by calculating standardized item alpha, intra-class correlation coefficients and kappa-statistics.

Results: DAS 28, SDAI and CDAI levels were significantly correlated to one another on group level. Internal consistency was the highest for the CDAI (alpha = 0.783) and the lowest for the DAS28 (alpha = 0.664). Kappa statistics revealed a substantial degree of congruence with respect to disease activity categorizing according to the three scales, with exceptions concerning the definition of remission. Testing for absolute agreement revealed nearly complete congruence between the SDAI and the CDAI values (average measure intra-class correlation: 0.9704; p < .0000). DAS 28 values and SDAI as well as CDAI values were also highly significant correlated (average measure intra-class correlations: 0.214 for DAS 28/SDAI and 0.237 for DAS 28/CDAI; both p's < .0000). Kappa to estimate the relationship between the disease activity categories according to the SDAI (SDAIC) and the EULAR, including the remission category, amounted to 0.551, for the relationship between CDAI disease activity categories (CDAIC) and the EULARC to 0.525. (p < 0,001, however below 0.65). The highest agreement could be found between the SDAIC and CDAIC as expected (kappa = 0,862 including remission criteria, 0,878 ignoring remission, both p's < 0,0001). Categorizing patients, ignoring remission, and summarizing low disease activity and remission into one category, however, revealed substantial agreement between the EULARC, the SDAIC and the CDAIC respectively (kappa = 0,707 and 0,671 respective, both p's < 0,0001). The percentage of patients in remission was similar when patients were assessed according to the SDAI or the CDAI. When applying the DAS 28, however, about 44 % more patients could have been categorized as being in remission. Seventy-eight of the 570 patients (13,7 %) fulfilled 0 TJ, 0 SJ and a CRP lower than 0,5 mg/dl. Zero up to 6 tender or up to 5 swollen joints are possible to achieve remission applying the DAS 28, whereas only a maximum of 2 tender or swollen joints are possible to reach this goal according to the SDAI or CDAI.

Conclusion: Congruence of disease activity categorizing according to DAS 28, SDAI and CDAI would be desirable for applying the new tools in daily routine. The recently revised SDAI-limits for disease activity and the respective CDAI thresholds proved to be in congruence with the EULARC in daily clinical routine. The SDAI and the CDAI were found to be more stringent to define remission. This fact seems to favour the SDAI and the CDAI for patient assessment in the future.

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Chronischer Kreuzschmerz – Beeinflussbarkeit in Abhängigkeit vom Chronifizierungsgrad

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Einleitung: Ziel der Untersuchung war es, bei Patienten mit chronischen Kreuzschmerzen die Änderung der Schmerzintensität durch ein dreiwöchiges stationäres Heilverfahren in Abhängigkeit vom Chronifizierungsgrad nach Gerbershagen und Wurmthaler zu eruieren.

Patienten und Methode: Die Fragebögen von 109 Patienten konnten ausgewertet werden. Es wurden Patienten mit chronischen Kreuzschmerzen (spezifische oder unspezifische Kreuzschmerzformen wurden inkludiert; ausgeschlossen waren lediglich Tumoren oder Spondylitiden als Ursache) befragt.

Definition des Kreuzschmerzes: Lokalisation der Schmerzen zwischen unteren Rippenbögen und unterer Gesäßfalte, mit oder ohne Ausstrahlung in ein oder beide Beine; Schmerzen seit mindestens 6 Monaten an mehr als der Hälfte der Tage.

Die Stadien der Schmerzchronifizierung wurden nach dem Chronifizierungsmodell (Fragebogen) nach Gerbershagen und Wurmthaler charakterisiert: klinische Kriterien, Schmerztopik und -ausbreitungstendenz, zeitliche Charakteristika des Schmerzempfindens, Medikamenteneinnahme und vorausgegangene rehabilitative bzw. operative Therapien spielen hier eine Rolle.

Bei den Patienten wurden zur besseren Stratifizierung Fragen nach Verschlechterung bzw. Grad der Verbesserung gestellt und somit vier Gruppen des Outcomes unterschieden.

Ergebnisse: siehe **Tabelle 4**

Diskussion: Das Ergebnis der Untersuchung ergab eine deutlich statistisch signifikant schlechtere Erfolgsrate eines rehabilitativen Heilverfahrens bei höherem Chronifizierungsgrad. Komorbiditäten wurden bei dieser Studie nicht berücksichtigt; diese spielen aber speziell beim Kreuzschmerz eine Rolle bei der Chronifizierung und sind Gegenstand weiterer Untersuchungen.

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Impact of TNF blocker therapy on disease activity, function and health status in ankylosing spondylitis in the community

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Background: Ankylosing spondylitis (AS) became a more treatable condition after the introduction of tumour necrosis factor (TNF) alpha blocking agents. Our objective was to evaluate the disease activity, function and health status of patients with AS in the community before and after the introduction of anti-TNF-alpha therapy.

Methods: In a cross-sectional survey in 2003 and after the introduction of TNF-blocking agents in 2006, we assessed the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index), and pain levels (0–10 on a visual analogue scale) in members of the Austrian AS Patients' Association.

Results: In the first survey in 2003, 668 AS patients (47.7 %) (469 male, 197 female; age 52 [12], mean [SD]) returned the questionnaire and reported a median (range) BASDAI of 4.8 (0.9–9.6), a median BASFI of 4.4 (1–10) and pain levels of 5 (1–10). In the second survey in 2006, 607 AS patients (50,5 %) (412 male, 195 female; age 47 [12]) returned the questionnaire and reported a median (range) BASDAI of 4.0 (0–9.2), a median BASFI of 3.8 (1–10) and pain levels of 4 (1–10). In 252 AS patients who participated in both surveys, we assessed the change of symptoms. In patients treated with TNF-alpha-blocking agents (infliximab or etanercept), clinical symptoms improved by 72 %, compared to 48 % (NSAID monotherapy), 34 % (sulfasalazin treatment) and 31 % (MTX) respectively. The mean BASDAI improved significantly ($p = 0.001$) from 4.8 (1.8) to 4.4 (2.1), the mean pain levels from 5 (1–10) to 4 (1–10), ($p = 0.000$). The BASFI did not improve significantly, as would be expected by the nature of the disease. In 23 patients with two observation time points, data before and after infliximab was available. Statistical analysis (Mann-Whitney U test) revealed a highly significant ($p = 0.003$) improvement of BASDAI in patients treated with infliximab with a mean (SD) of 1.96 (2.08).

Conclusion: After the introduction of anti-TNF therapy AS disease activity and pain intensity improved significantly in the community and at the individual level.

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35jähriger Mann mit Hüftschmerzen und Thrombopenie

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Tabelle 4: Wagner E. Änderung der Schmerzintensität in Abhängigkeit vom Chronifizierungsgrad (Prozentsätze beziehen sich auf Zahl der Patienten pro Chronifizierungsgrad)

Schmerz	Chronifizierungsgrad I	II	III
Verschlechterung	0	0	0
Keine Änderung	3 (12,5 %)	14 (23,7 %)	5 (19,2 %)
Leichte Besserung	2 (8,3 %)	5 (8,5 %)	11 (42,3 %)
Starke Besserung	19 (79,2 %)	40 (67,8 %)	10 (38,5 %)
	24	59	26

Im Sommer 2006 treten bei einem bisher gesunden 35jährigen Mann belastungsabhängige Schmerzen in der rechten Hüfte auf. Im Röntgen imponiert der gesamte Beckenknochen inhomogen. Eine MR-Tomographie des rechten Hüftgelenkes zeigt eine inhomogene Strukturalteration im Bereich des gesamten Os ilium, Os pubis und Os ischii sowie des rechten Femurschafts ohne Zeichen einer Knochendestruktion. Neben einer homogenen Splenomegalie mit 13 x 9,5 cm liegt eine Thombopenie (99 G/l) vor. Die Biopsie an der Spina iliaca posterior superior dextra ergibt eine Knochenmarks- und Knochennekrose. In der FDG-PET finden sich diffuse Speicherungen in der gesamten Wirbelsäule, im Becken, im Bereich des Rippenskeletts und in den proximalen Extremitäten, weiters eine diffuse Speicherung in der vergrößerten Milz. Durch die Biopsie an der Spina iliaca posterior superior sinistra lassen sich neben einer unauffälligen Hämatopoese Speicherzellen nachweisen. Die Verdachtsdiagnose eines Morbus Gaucher wird durch die Bestimmung der Glukozerebrosidase (0,49 nMol/mg, Normwert: 0,7–3,99) und der Chitotriodidase (11 441 nMol/ml/h, Kontrollwert = 163) bestätigt und die Indikation zur raschen Enzymersatztherapie mit Imiglucerase gestellt. Alle zwei Wochen erhält der Patient 40 U/kg KG Cerezyme®. Bereits 6 Monate nach Therapieeinleitung kommt es zur Normalisierung der Thrombopenie (157 G/l).

Basiswissenschaftliche Abstracts

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CCR2-deficient mice are osteopetrotic due to impaired osteoclast development and function

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Background: Enhanced osteoclast (OC) activity or uncoupling of osteoclastic bone resorption from bone formation results in focal or generalized bone loss. This is a characteristic feature of several bone diseases such as osteoporosis or Paget disease. Beside the two major osteoclastogenic cytokines M-CSF and RANKL, other cytokines and chemokines are active contributors in OC formation and function. Among them monocyte chemotactic protein 1 (MCP-1), signalling through its receptor CCR2 might also play a role in osteoclastogenesis.

Methods: The bone phenotype of wild-type and CCR2$^{-/-}$ was investigated. Therefore 2 µm sections of decalcified paraffin-embedded left tibiae were stained with TRAP for detecting OCs. For histomorphometry, right tibiae were embedded in methyl-methacrylat and stained with von Kossa. Morphometry of metaphyses was performed according to international standards.

For in vitro osteoclast formation bone marrow macrophages (BMM) were used. Bone marrow cells were cultured with M-CSF over 6 days. The generated OC precursors (pOC) were then kept under osteoclastogenetic conditions (30 ng/ml M-CSF and 50 ng/ml RANKL). In some experiments MCP-1 or TNF-alpha were added to the culture to enhance OC formation. TRAP staining was performed to detect levels of OC and their mononuclear precursors.

Results: Mice lacking the chemokine receptor, exhibited a marked increase of bone volume (+ 40 %) compared to their wild-type littermates. In line with this finding, bone mineral density (BMD) measured by micro CT was also elevated in CCR2 deficient mice. The increase of BMD in CCR2$^{-/-}$ mice was accompanied by a 40 % decrease in OC numbers, clearly demonstrating that the lack of CCR2 resulted in an osteopetrotic phenotype. To investigate whether or not CCR2 is also essential for OC function, we generated OCs in vitro. Osteoclastogenesis was clearly reduced in BMMs lacking the chemokine receptor. By adding recombinant MCP-1 elevated OC numbers could be seen only in cultures derived from wild-type animals. In contrast, stimulation of CCR2$^{-/-}$ pOCs with TNF-alpha, resulted in elevated OC numbers equal to the increase of wild-type cultured pOCs.

To test if CCR2 has also an influence on the capacity of OCs to resorb bone CCR2$^{-/-}$ and wild-type OCs were cultured on bovine bone slices after stimulation with M-CSF and RANKL. A marked reduction of bone resorption by CCR2$^{-/-}$ OCs clearly points out that this receptor is not only important for OC development but also function. Taken together this data clearly indicate an important role of the MCP-1/CCR2 pathway for osteoclast generation and function in vitro and in vivo.

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Divergente Rollen der beiden TNF-Rezeptoren bei Arthritis

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Einleitung: TNF ist ein Zytokin, das bei der Entstehung und Perpetuierung von rheumatoider Arthritis (RA) und den damit verbundenen Knochenschäden von zentraler Bedeutung ist. Die Wirkung von TNF wird von zwei Rezeptoren vermittelt (TNFR1 und TNFR2), deren respektive Bedeutung in der Genese der RA allerdings noch kaum untersucht wurde.

Methoden und Resultate: Wir konnten jetzt in einem anerkannten Mausmodell der RA zeigen, daß TNFR1 die arthrithogene Wirkung von TNF mediiert und in den Tieren, denen dieser Rezeptor fehlt, eine mildere Arthritis entwickelt als Kontrollen. TNFR2 scheint jedoch einen protektiven Einfluß auf die Entstehung der Arthritis zu haben, bei einem Fehlen des Rezeptors zeigte sich eine deutlich aggressivere Arthritis in Hinblick auf lokale Knochendestruktion. In vitro zeigen Makrophagen, die aus den jeweiligen Knock-outs gewonnen wurden, unterschiedliche Fähigkeit, sich zu knochendestruierenden Osteoklasten zu differenzieren.

Schlußfolgerung: Derzeitige therapeutische Ansätze blockieren das Zytokin TNF. Aufgrund unserer Studie wäre aber eine selektive Blockade des TNFR1 eventuell eine effektivere Behandlung zur Behandlung der RA.

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Differentially regulated expression of growth and differentiation factor-5 and bone morphogenetic protein-7 in articular cartilage and synovium in chronic arthritis – potential importance for cartilage breakdown and synovial hypertrophy

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Objective: To examine whether the endogenous expression of growth and differentiation factor (GDF)-5 and bone morphogenetic protein (BMP)-7 is altered in arthritic cartilage and synovium of human tumor necrosis factor α transgenic (hTNFtg) mice and to investigate the response of hTNFtg chondrocytes as well as fibroblast-like synoviocytes (FLS) to these morphogens in vitro.

Methods: Analyses were performed in hTNFtg mice, which suffer from chronic destructive arthritis and wild type (WT) mice. Expression of GDF-5 and BMP-7 in articular cartilage and synovium was examined by real-time PCR and immunohistochemistry. hTNFtg cartilage explants, chondrocyte and FLS monolayer cultures were assessed for basal matrix biosynthesis as well as growth factor responsiveness using [^{35}S] sulfate incorporation assays. Furthermore, DNA content/cell proliferation rate was measured.

Results: The expression of GDF-5 and BMP-7 was decreased in articular cartilage from hTNFtg mice, while arthritic synovium displayed an increased expression of these morphogens compared to WT controls. Isotope incorporation revealed a marked reduction of matrix synthesis in hTNFtg cartilage as well as a decrease in responsiveness to GDF-5 and BMP-7. DNA content in arthritic cartilage did not change in comparison to WT animals. In hTNFtg FLS growth factor-stimulation increased cell proliferation rate and extracellular matrix production.

Conclusion: In this murine model of TNFα-mediated arthritis the expression of GDF-5 and BMP-7 in articular cartilage and synovium was regulated differentially. While in articular cartilage a downregulation of GDF-5 and BMP-7, which aim to maintain its integrity, potentially compromises tissue repair, the increased expression of GDF-5 and BMP-7 in the synovium might contribute to synovial hypertrophy.

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Increased expression of discoidin domain receptor 2 is linked to the degree of cartilage damage in human knee joints: a potential role in osteoarthritis pathogenesis

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Objective: To investigate the relationship between increased expression of discoidin domain receptor 2 (DDR2) and cartilage damage in osteoarthritis (OA).

Methods: Full thickness cartilage tissue samples from 16 human knee joints were obtained and the grade of cartilage damage was evaluated according to the Mankin scoring system. The expression of DDR2, matrix-metalloproteinase-13 (MMP-13), as well as MMP-derived type II collagen fragments was visualized immunohistochemically. Moreover, upon stimulation with either type II collagen or gelatine mRNA levels of DDR2 and MMP-13 in primary human articular chondrocytes were assessed by real-time PCR.

Results: Immunohistochemistry showed an increase in DDR2 expression in human articular cartilage, which was correlated to the degree of tissue damage. In parallel, the extent of MMP-13 and type II collagen breakdown products was elevated as a function of increased DDR2 expression and cartilage damage. Furthermore, in vitro experiments revealed an upregulation of both DDR2 and MMP-13 mRNAs in human articular chondrocytes after stimulation with type II collagen.

Conclusion: Our data indicate that the three factors, DDR2 expression, MMP-13 expression and the degree of cartilage damage, are linked in a way that DDR2 promotes tissue catabolism and vice versa tissue degradation promotes DDR2 upregulation and activation. Thus, the perpetuation of DDR2 expression and activation can be seen as a vicious circle that ultimately leads to cartilage destruction in OA.

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Foxp3 expression in $CD4^+$ T cells of patients with systemic lupus erythematosus (SLE): activation or regulation?

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Purpose: The transcription factor Foxp3 is regarded as highly specific for the phenotypic characterization of $CD4^+CD25^+$ regulatory T cells (Treg). At least in the human system, however, expression of both Foxp3 and CD25 can be induced in vitro upon T cell activation. Little however is known about the significance of Foxp3 expression under autoimmune conditions with chronic T cell activation. This tempted us to evaluate Foxp3 expression in SLE patients as compared to healthy controls (HC).

Methods: Proportions of peripheral blood $CD4^+Foxp3^+$ T cells and $CD4^+CD25^{high}$ T cells were determined in active and inactive SLE patients as compared to HC by flow cytometry. Comparative analysis of % $CD4^+Foxp3^+$ T cells and % $CD4^+CD25^{high}$ T cells with clinical disease activity and T cell activation marker molecule expression were performed. Finally, the induction of Foxp3 expression was analyzed upon T cell activation in vitro.

Results: Proportions of $CD4^+Foxp3^+$ T cells were significantly increased in SLE patients as compared to HC and a significant correlation with the % $CD4^+Foxp3^+$ T cells was observed for the clinical disease activity and the % $CD4^+CD69^+$ T cells. On the other hand, proportions of $CD4^+CD25^{high}$ were decreased in SLE and an inverse, albeit not significant, correlation was observed with the clinical disease activity. No correlation with the % $CD4^+CD69^+$ T cells was observed. In addition, in vitro activation of T cells induced Foxp3 expression.

Conclusion: Our data suggest that the expression of Foxp3 on $CD4^+$ T cells in SLE patients, at least to some extent, reflects the activation of $CD4^+$ T cells due to underlying disease activity and does not necessarily indicate a functional regulatory T cell capacity.

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NKG2D stimulated T cell autoreactivity in polymyalgia rheumatica and giant cell arteritis

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Purpose: To assess the functional expression of NKG2D on CD4+ and CD8+ T-cells in polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) and to test the expression of NKG2D ligands in temporal arteries from PMR and GCA patients.

Methods: Patients with PMR (n = 78) and GCA (n = 16) and healthy controls (HC, n = 64) were enrolled prospectively. CD4+ and CD8+ T-cells were isolated from PBMCs by MACS-technology. Regulation of NKG2D expression was assessed using human TNF-α 20 ng/mL), IL-15 (20 ng/mL) IL-18 (100 ng/mL), IFN-γ 10 ng/mL) and solid-phase anti-CD3. The effect of NKG2D co-stimulation was tested in proliferation and cytokine production assays using the fluorescent dye CFSE and intracellular cytokine staining with anti-IFN-γ and anti-TNF-α mAbs, respectively. Expression of MICA, MICB and ULBP1-3 were determined in temporal arteries from PMR and GCA patients by real time-PCR and immunohistochemistry.

Results: The frequency of CD4+CD28- and CD8+CD28- T-cells was increased in PMR and GCA patients compared to HC. In the CD4+ T-cell subset, the median expression of NKG2D was higher on CD28- than on CD28+ T-cells (PMR: 15.0 % vs 1.2 %, $p < 0.001$; GCA: 12.2 % vs 1.1 %, $p = 0.093$). NKG2D expression did not differ between CD8+CD28- and CD8+CD28+ T-cells. Stimulation with anti-CD3 induced up-regulation of NKG2D on CD4+CD28- and CD4+CD28+ T-cells that was highest after 12 hours (mean fluorescence intensity [MFI] 18.6 vs 12.7 at baseline; $p < 0.05$) and 6 hours, respectively. Stimulation of T-cells with TNF-α and IL-15 but not IL-18 and IFN-γ resulted in an up-regulation of NKG2D on CD4+CD28- and CD8+CD28- T-cells although kinetics was slower compared to anti-CD3 stimulation. After 48 hours of stimulation NKG2D expression on CD4+CD28- and CD8+CD28- T-cells was highest compared to baseline (MFI 22.4 vs 16.6; $p < 0.05$ and 58.3 vs 50.2; $p < 0.05$, respectively). In proliferation assays, NKG2D crosslinkage augmented anti-CD3 induced proliferation of CD8+CD28 -T-cells (50.0 % vs 37.0 %; $p < 0.05$) and CD8+CD28+ T-cells (69.9 % vs 40.6 %; $p < 0.05$). NKG2D also co-stimulated IFN-γ production of CD4+CD28- T-cells (MFI 53.9 vs 42.3; $p < 0.05$), CD8+CD28- T-cells (34.2 vs 21.5; $p < 0.05$) and CD8+CD28+ T-cells (36.7 vs 21.4; $p < 0.05$). TNF-α production was influenced by NKG2D only in CD8+CD28- and CD8+CD28+ T-cells. Expression of MICA, MICB and ULBP2 mRNA was increased in temporal arteries from GCA (3.46 fold ± 1.69, 4.92 ± 1.79 and 16.68 ± 1.82, respectively ; $p < 0.05$ each) and PMR patients (2.31 ± 1.55, 3.97 ± 2.39 and 19.03 ± 1.94, respectively; $p < 0.05$ each) compared to carotid arteries from controls. Immunohistological studies showed MICA to be located in the media but not in the intima or adventitial layer.

Conclusions: These data demonstrate the functional expression of NKG2D on CD4+CD28-, CD8+CD28- and CD8+CD28+ T-cells and presence of NKG2D- ligands in temporal arteries as an alternative pathway for autoreactive T cell stimulation in PMR and GCA.

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Rheumatoid factors, but not antibodies against citrullinated peptides are modulated by TNF-α blocking therapy in rheumatoid arthritis

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Background: Studies on the determination of anti-cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor (RF) as serologic parameters to monitor disease activity in patients with rheumatoid arthritis (RA) treated with TNF-α blocking agents have reported contradictory results.

Objective: The aim of this retrospective study was to analyze whether serum levels of second generation anti-CCP (anti-CCP2), anti-modified citrullinated vimentin (anti-MCV) and anti-cyclic citrullinated peptide 3 (anti-CCP3) antibodies are influenced by TNF-α blocking treatment and/or may predict treatment response in patients with RA. Results were then compared with IgG-RF, IgA-RF and IgM-RF.

Methods: This study was carried out on 42 RA patients either treated with infliximab (n = 11), etanercept (n = 7) or adalimumab (n = 24). Serum anti-CCP2, anti-MCV, anti-CCP3, IgG-RF, IgA-RF and IgM-RF levels were tested before and six month after starting a TNF-α blocking treatment using commercially available ELISA kits.

Results: A significant reduction of IgG-RF (72 U/mL [range 6–780] to 40 U/mL [6–583], $p = 0.014$), IgA-RF (50 U/mL [3–677] to 34 U/mL [2–677], $p = 0.042$) and IgM-RF titres (191 [3–529] to 79 [4–500], $p = 0.014$) but not of anti-CCP2, anti-MCV and anti-CCP3 was observed in EULAR responders after 6 months of treatment. Concerning prediction of treatment response, receiving operating characteristic curve analysis revealed a significant area under the curve (AUC) for the difference in IgA-RF concentration before and after therapy (AUC 0.724; 95 % CI 0.547–0.901; $p = 0.027$) but not for the other RF and anti-citrullinated peptide tests. None of the RF and anti-citrullinated peptide tests was associated with treatment response using single predictor and covariate-adjusted logistic regression models.

Conclusion: According to the clinical response, anti-TNF-α agents reduce IgG-RF, IgA-RF, IgM-RF levels. The difference in IgA-RF concentration before and after treatment may have a limited value to predict an EULAR-response, but none of the other RF and anti-citrullinated peptide tests.

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Dickkopf-1 is a master regulator of joint remodelling

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Background: Degenerative and inflammatory joint diseases lead to a destruction of the joint architecture. Whereas degenerative osteoarthritis results in the formation of new

bone, rheumatoid arthritis leads to bone resorption. The molecular basis of these different patterns of joint disease is unknown.

Methods: By inhibiting Dickkopf-1 (DKK-1), a regulatory molecule of the Wnt pathway, we were able to reverse the bone-destructive pattern of a mouse model of rheumatoid arthritis to the bone-forming pattern of osteoarthritis.

Results: In this way, no overall bone erosion resulted, although bony nodules, so-called osteophytes, did form. We identified tumor necrosis factor- (TNF) as a key inducer of DKK-1 in the mouse inflammatory arthritis model and in human rheumatoid arthritis.

Conclusion: These results suggest that the Wnt pathway is a key regulator of joint remodelling.

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Endothelial progenitor cells in active rheumatoid arthritis: Effects of TNF and of glucocorticoid therapy

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Objectives: To study the effects of short term intermediate dose glucocorticoid therapy in patients with active rheumatoid arthritis (RA) on circulating endothelial progenitor cells (EPC), which are known to influence cardiovascular risk, and to elucidate mechanisms potentially responsible for the reduction of EPCs in patients with active RA.

Methods: EPC were quantified in 29 patients with active RA by flow cytometry, colony forming unit (CFU) and circulating angiogenic cell (CAC) assays before and after 7 days of intermediate dose glucocorticoid therapy. CFU from RA patients and from healthy referents (HR) were cultured in vitro in the absence or presence of dexamethasone (Dex) and/or TNF.

Results: After one week of glucocorticoid therapy, EPC increased from 0.026 ± 0.003 % to 0.053 ± 0.010 % ($p < 0.01$), and from 12 ± 4 to 27 ± 7 CFU/well ($p < 0.02$); CAC also increased from 7 ± 2 to 29 ± 8 cells/high power field ($p < 0.05$). In parallel, disease activity decreased significantly after glucocorticoid treatment. TNF serum levels also decreased from 36 ± 10 to 14 ± 6 pg/ml ($p < 0.0001$). Addition of Dex to the RA CFU led to a significant increase of mean CFU counts, whereas addition of TNF induced a decrease of CFU.

Conclusions: Our data indicate that TNF may be at least partly responsible for the reduction of EPC seen in RA patients. Intermediate doses of glucocorticoids for a short period of time, aside of reducing disease activity, significantly increase circulating EPC.

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Systemic lupus erythematosus is associated with normal circulating endothelial progenitor cell levels but impaired EPC migration behaviour

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Background: Systemic lupus erythematosus (SLE) is characterized by an increased cardiovascular risk (CVR). Since levels of circulating endothelial progenitor cells (EPC) have been described to serve as a biomarker for the CVR and are known to be depleted in various (inflammatory) diseases, we were interested if SLE would also be associated with altered peripheral EPC levels and/or functional abnormalities of these cells.

Patients and Methods: EPC were quantified in 31 female SLE patients with diverse stages of SLE activity and in 14 age matched female healthy controls (HC) by FACS analysis (by staining for CD34/KDR/CD133 within the lymphocyte gate) as well as by the colony forming unit (CFU)-assay. Furthermore, EPC migration capacity was tested by a transwell migration assay and CFU were cultured in the presence of diverse doses of chloroquine. Moreover, serum levels of the following cytokines and growth factors were detected by ELISA-technique: TNF, IL-6, VEGF and bFGF.

Results: EPC levels in SLE did not differ from HC as detected by FACS (0.045 ± 0.006 % vs 0.036 ± 0.007 % within the lymphocyte gate) and by the CFU assay (18 ± 3 vs 15 ± 2 colonies/well). No correlation with regard to disease activity could be observed. In contrast, the migration capacity of cells from SLE patients was significantly affected (56 ± 6 migrated vs 121 ± 28 CAC/random microscopic field, $p < 0.02$). Within the SLE patients, those treated with chloroquine exhibited significantly lower EPC levels than those without immunosuppression as detected by FACS analysis (0.058 ± 0.005 % vs 0.024 ± 0.008 %, $p < 0.05$). In SLE as well as in HC, addition of chloroquine also led to a decreased colony formation in vitro: 22 ± 2 CFU/well with medium alone vs 4 ± 3 with 15 µM chloroquine ($p < 0.001$) in SLE and 30 ± 6 CFU/well vs 5 ± 3 ($p < 0.05$, 15 µM chloroquine).

Serum levels of TNF were found to be significantly increased in SLE (54 ± 4 pg/ml vs 4 ± 4 pg/ml in HC, $p < 0.0005$). Furthermore, in SLE we observed a significant correlation of VEGF serum levels and circulating EPC as detected by FACS ($r = 0.383$, $p < 0.05$), confirming the proangiogenic/-vasculogenic potential of this growth-factor also in SLE.

Conclusions: Taken together, our data reveal, that EPC are significantly affected in SLE. The observation that the transmigration capacity is decreased, while circulating EPC levels are in the range of HC, indicates that the total "EPC-pool" might be anyhow depleted. Moreover, the in vitro- as well as the in vitro results show that antimalarials might induce a reduction of peripheral EPC levels.

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The human autoantigen hnRNP-A2 (RA33) is a major inducer of autoimmunity in rats with pristane-induced arthritis and may activate innate immunity via TLR7

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Introduction: Pristane-induced arthritis (PIA) in rats is considered an excellent model for rheumatoid arthritis (RA) since it fulfils the criteria for RA including a chronic relapsing disease course and is not dependent on immunization with exogenous antigen. Although the adjuvant pristane is not im-

munogenic, the disease is MHC associated and dependent on the activation of (autoreactive) T cells. However, so far it has not been possible to link the immune response to joint antigens or other endogenous components. It was therefore the aim of this study to analyse B- and T-cell responses to candidate autoantigens such as rheumatoid factor, heat shock proteins, citrullinated proteins, glucose-6-phosphate isomerase, and hnRNP-A2 (RA33) in rats with PIA.

Methods: AutoAb against RA-associated autoantigens were determined by ELISA and immunoblotting. Cytokine secretion upon coculture with candidate autoantigens by rat splenocytes and lymph node cells as well as by splenocytes from MyD88^{ko} and WT mice was determined by ELISA. PIA was histologically characterized by toluidine blue, hematoxylin and eosine, and tartrate resistant acid phosphatase (TRAP) staining expression of hnRNP-A2 in joints and organs of rats was analysed by real time PCR, immunohistochemistry and western blotting.

Results: Autoantibodies to hnRNP-A2 are present in pristane-injected rats already one week before disease onset, reaching maximum levels during the acute phase of PIA. Furthermore, also pronounced T-cell reactivity to hnRNP-A2 showing a Th1-like phenotype can be observed prior to the appearance of symptoms of arthritis. Surprisingly, hnRNP-A2 was also able to stimulate non pristane-primed lymph node cells to produce inflammatory cytokines. The cytokine response was produced by monocytes/macrophages in a MyD88-dependent manner suggesting involvement of toll like receptors (TLR). Mammalian ribonucleoprotein (RNP) particles such as the spliceosomal small nuclear RNPs have already been shown to stimulate TLR7 and TLR8 as well as to activate innate immune cells [Vollmer et al. J Exp Med 2005; 202: 1575]. A TLR ligand screening suggested that TLR7 might indeed also be involved in the response to hnRNP-A2.

Discussion: The early presence of humoral and cellular autoimmune responses to hnRNP-A2, its abundant expression in the inflamed joint and, importantly, its capability to activate the innate immune system suggests this autoantigen to play a major role in the pathogenesis of PIA and possibly also in rheumatoid arthritis.

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TNF promotes remodelling of cadherin-11 intercellular junctions and condensation of fibroblast-like synoviocytes

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Cadherin-11 is a homophilic adhesion molecule that is expressed on fibroblast-like synoviocytes (FLS). Cadherins mediate tissue morphogenesis during development and maintenance of tissue architecture in adults. Recently, cadherin-11 was found to participate in tissue and lining layer formation in the synovium. Here we demonstrate that TNF promotes reorganization of cadherin-11 intercellular junctions and cellular condensation of fibroblast-like synoviocytes.

To investigate a role for cadherin-11 in mediating mesenchymal tissue reorganization and pannus formation in arthritis, we have analyzed the expression of cadherin-11 in diarthrodial joints of patients with rheumatoid arthritis. Immunohistochemistry revealed cadherin-11 expression in the synovial lining layer and in some cells of the sublining area. Strikingly, cadherin-11 was also expressed in condensed fibroblast-like cells at the erosive interface between pannus tissue and cartilage. To test the inflammatory response of FLS in a simplified model of the complex synovial microenvironment, we stimulated 3-dimensional micromass synovial organ cultures with tumor necrosis factor (TNF) or platelet derived growth factor (PDGF). When unstimulated or stimulated with PDGF, the FLS formed a lining layer at the micromass surface whereas the sublining FLS were loosely organized.
By contrast, TNF stimulation induced pronounced FLS condensation not only at the surface lining layer but also in the sublining area. Thus, TNF stimulation had a profound impact on the cellular organization in this model system. Since cadherin-11 mediates homophilic adhesion of FLS, we explored the structure of intercellular junctions in TNF or PDGF stimulated cultured FLS. Using indirect immunofluorescence and confocal microscopy, we found that unstimulated or PDGF stimulated FLS connected to one another via filopodia-like processes that interdigitated to form a cadherin-11 adhesion zipper. In TNF stimulated FLS, the cells were intimately connected and the anti-cadherin-11 antibody labelled a mostly linear or jagged line of intercellular junctions. These studies suggest a role for cadherin-11 in TNF induced reorganization of FLS and may provide insight into FLS behavior and function in arthritis, especially rheumatoid arthritis.

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Multizentrische Evaluation des AxSYM-Anti-CCP-Tests

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Hintergrund: Innerhalb der letzten Jahre hat eine zunehmende Zahl an Publikationen berichtet, daß der Anti-CCP (cyclisch citrullinierte Peptide)- Test der Marker der Wahl für die Diagnose der frühen rheumatoiden Arthritis (RA) ist. Diese Beobachtungen basieren auf der hohen Spezifität des Anti-CCP-Tests gekoppelt mit einer Sensitivität, die dem weitverbreiteten Rheumafaktortest (RF) vergleichbar ist. Ferner wurde über Anti-CCP2-Antikörper berichtet, daß sie einen unabhängigen Prädiktor für Gefäßschädigung und Krankheitsprogression darstellen.

Ziel der Studie: Anti-CCP2-Messungen werden fast ausschließlich mit manuellen ELISA-Methoden durchgeführt – mit den dazugehörigen Nachteilen. Vor kurzem wurde ein neuer vollautomatisierter Assay zur Anti-CCP2-Bestimmung eingeführt. Wir berichten über die AxSYM-Snti-CCP-Evaluation an zwei Zentren.

Methode: Die Evaluationen wurden an der Klinischen Abteilung für Allgemeine Innere Medizin in Innsbruck, Österreich, und am Department für Klinische Chemie und Laboratoriumsmedizin der Isala Klinieken Zwolle, Niederlande, durchgeführt. Die AxSYM-Anti-CCP2-Bestimmung erfolgte an insgesamt 404 Proben von 170 Patienten mit klinisch bestätigter RA, 60 Proben von asymptomatischen Personen und 174 Proben aus einer Kohorte, die als nicht-RA (Arthrose, Psoriasisarthritis, Fibromyalgie, andere Bindegewebserkrankungen) beurteilt wurden. In beiden Zentren wurden die Proben auch mit der Phadia-Elia-CCP-Methode gemessen. Die kombinierte Probenbestimmung der beiden Zentren war wie in **Tabelle 5** dargestellt.

Tabelle 5: Klotz W et al.

Probe	n	AxSYM-Anti-CCP	Elia-CCP-positiv
Gesund	60	0	0
Nicht-RA	174	7	8
RA	170	108	109
% Klinische Sensitivität		63,5	64,1
% Klinische Spezifität		97,0	96,6

Schlußfolgerung: Die Ergebnisse dieser Zwei-Zentren-Studie zeigen, daß der neue vollautomatisierte AxSYM-Anti-CCP-Test mit publizierten Berichten übereinstimmt und in hohem Maß mit der automatisierten Elia-CCP-Methode vergleichbar ist. Die volle Automatisierung und der rasche Probendurchsatz am AxSYM machen diesen Test zu einer idealen Basis für die routinemäßige Bestimmung dieses wichtigen Parameters.

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Crosstalk between IL-1 and sphingolipids: sphingosine-1-phosphate abrogates nitric oxide production and loss of glycosaminoglycans in bovine chondrocytes

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Objective: Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid, known to influence inflammation and wound healing and high levels of S1P are found in osteoarthritic joints. S1P potently stimulates chondrocyte proliferation by binding to its specific receptors. In our study we focused on the interactions of S1P and Interleukin 1 (IL-1).

Methods: Human cartilage specimens were obtained from patients undergoing total knee joint replacement. Specimens were formalin fixed and paraffin embedded. S1P receptor isotypes 1, 2 and 3 were detected by immunohistochemistry using the labelled streptavidin biotin method. Cartilage explants were taken from bovine metacarpophalangeal joints and chondrocytes were isolated using collagenase B. Cells grown in monolayer and cartilage explant were cultured in Ham's F-12/DMEM (1:1) and 10 % FCS. Loss of glycosaminoglycans (GAG) from cartilage explants after 24 h of treatment with 20 ng/ml IL-1β alone or in combination with 0.1 µM up to 3 µM S1P was determined using dimethyl-mehylen blue assay. Cultured chondrocytes were serum starved for 24 hours and incubated with 20 ng/ml IL-1β alone or in combination with 0.1 µM up to 3 µM S1P. Expression of inducible nitric oxide synthase (iNOS), aggrecanase-1, matrixmetalloproteinase-13 (MMP-13), tissue inhibitor of metalloproteases 1 (TIMP-1) and COX-2 was evaluated using real-time PCR. Western immunoblot was performed to confirm mRNA expression data.

Results: S1P decreased iNOS expression in unstimulated and IL-1β stimulated chondrocytes in a dose dependent manner. The inductive effect of IL-1β on iNOS mRNA was significantly inhibited by S1P ($p < 0.05$). At concentrations of 0.1 µM S1P reduced the stimulatory effect of IL-1β by 50 ± 3 % (mean ± SD). Furthermore, concentrations of 0.5 µM S1P reduced iNOS expression to 19 ± 10 % (mean ± SD). Westernblot experiments confirmed these results. iNOS activity induced by IL-1β was reduced to 25 ± 13 % (mean ± SD, $p < 0.05$) upon treatment with 0.5 µM S1P. Furthermore IL-1β mediated GAG depletion from cartilage explants was completely abrogated at a concentration of 3 µM S1P ($p < 0.05$), resulting in GAG loss equal to untreated controls.

Conclusion: In addition to the proliferative effect of S1P, our data demonstrate that S1P blocks iNOS expression, NO formation and GAG depletion in IL-1β treated chondrocytes. S1P might therefore be a candidate to target ongoing IL-1 induced damage in osteoarthritic joints.

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Mechanisms of selective activation of HAS1 by Epstein-Barr virus and synthetic viral analogs

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Introduction: Hyaluronan (HA) plays an important role in inflammation and cell migration by acting as the main ligand for CD44. Unfettered HA production is also a hallmark of rheumatoid arthritis. Three genes encode hyaluronan synthases (HAS). Whether and to what degree viral infections affect HAS transcription and HA release in synoviocytes isolated from arthritis patients is the focus of this study.

Methods: Signalling pathways and the effectiveness of live Epstein-Barr virus (EBV) as well as synthetic viral analogs as inducers of HAS transcription and HA production were tested by real time RT-PCR, electrophoretic mobility shift assays, western blots, and ELISA-like assays.

Results: EBV treated fibroblast-like synoviocytes significantly increase HA production and release. Real time RT-PCR data show that steady state HAS1 mRNA levels are significantly elevated in virus treated cells while mRNA levels for the genes HAS2 and HAS3 remain unchanged. As to the mechanism of virus induced HAS1 transcription, data are presented that imply that among the double and single stranded polynucleotides tested, homopolymeric polycytidylic structures are the most potent inducers of HAS1 transcription and HA release while homopolymeric polyinosinic acid is without effect. Analyses of virus induced signal cascades, utilizing chemical inhibitors of MAPK and overexpressing mutated IKK and IκB, revealed that the MAPK p38 as well as the transcription factor NF-κB are essential for virus induced activation of HAS1.

Conclusions: The presented data point at HAS1 as being regulated in many ways similar to proinflammatory gene. The data also seem to implicate that it is the product of HAS1 that acts as ligand for CD44-HA mediated cell migration.

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In vitro and in vivo H_2S is a potent inducer of proinflammatory genes: HO-1 and HSP70 are unable to prevent H_2S mediated gene activation

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Introduction: A stress response, induced by various means, has the potential to be beneficial for patients. We tested whether hydrogen sulfide (H_2S), an important signalling molecule, also relevant in certain therapies, but known for detrimental effects, might induce a so called protective stress response.

Methods: Data were generated using fibroblast-like synoviocytes treated with sodium hydrosulfide and mice exposed to a H_2S atmosphere of a sulfur spa.

Results: A profound and long lasting induction of the stress-response could be observed in response to H_2S in in-vitro as well as in-vivo experiments. However, despite the sustained presence of large amounts of HO-1 and HSP70, proinflammatory effects of exposure to IL-1β or H_2S itself were not ameliorated. On the contrary, a number of undesirable effects were noted at H_2S concentrations significantly lower than the current maximal allowable concentration (MAC). COX-2, IL-8, IL-1α, IL-1β, and TNF-α were dose dependently elevated. Also important is that short-term exposure to H_2S resulted in the activation of all three MAPK. In addition, mitochondrial activity was significantly impaired at H_2S concentrations considerably lower than the current MAC. The transcription factor NF-κB is essential for the activation of most proinflammatory genes. However, a number of experiments demonstrate that H_2S activates proinflammatory genes through non-NF-κB-dependent pathways. Stress proteins reportedly act by blocking NF-κB activation, a mechanism that would explain the inability of stress proteins to prevent H_2S mediated inflammatory processes.

Conclusions: The presented data, showing MAPK activation, NF-κB-independent activation of a number of proinflammatory genes and detrimental effects on mitochondria seem relevant for individuals exposed to H_2S as well for a better understanding of the (patho)physiological effects of H_2S.

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Dual mechanisms of hyperthermia mediated anti-inflammatory effects: Independent of its effects on NF-kappaB, short term hyperthermia prevents gene activation by selectively blocking the MAPK p38

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Introduction: Heat shock proteins, activated by hyperthermia (HT) or by other means, have long been known for their potential to protect cells and organisms. In general, it is thought that HT acts by upregulating heat shock proteins such as HO-1 or HSP70. We demonstrated earlier that HT suppresses transcription and translation of a number of proinflammatory genes in fibroblast like synoviocytes (FLS) isolated from rheumatoid arthritis patients.

Methods: Western blot, real-time RT-PCR, MAPK-inhibitors etc were used to analyze intracellular signalling pathways, protein expression and transcriptional activation/ repression of proinflammatory genes by balneological means.

Results: Data imply that short term HT not only acts by preventing the activation of NF-κB, a transcription factor of nearly universal importance for the activation of proinflammatory genes, but also by blocking the activation of the MAPK p38. We present data that show that the effects of HT on p38 are clearly independent of HT effects on NF-κB. This is demonstrated by the ability of short term HT to prevent IL-1β induced activation of MAPK p38 dependent, but NF-κB independent genes. In general it is assumed that the protective effects of HT are mediated by de novo synthesis of a number of heat shock proteins. However, our novel findings imply the need to distinguish early and late acting mechanisms of short term HT. Neither a recovery period nor de novo protein synthesis is essential for the early protective effects of HT.

Conclusions: The effectiveness of short term HT preventing the activation of two of the most important signalling pathways leading to inflammation and the relative ease by which the temperature in joints of arthritis patients might be modulated, seemingly offer an appealing opportunity to prevent or diminish inflammation by balneological means.

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