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Rheumatoid arthritis: the influence of disease activity on clinical and serological parameters

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Contents

Abbreviation

AAB	autoantibody
ACPA	antibodies against cyclic citrullinated peptides
ACR	American College of Rheumatology
CCP	cyclic citrullinated peptides
CDAI	clinical disease activity index
CRP	c-reactive protein
CRT	chair-rising test
DAS-28	disease activity score 28
DIP	distal interphalangeal
DMARDS	disease modifying anti-rheumatic drugs
EGA	evaluator global assessment of disease activity
ELISA	enzyme linked immunosorbent assay
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HAQ	health assessment questionnaire
HAQ DI	health assessment questionnaire disability index
IG	immunoglobulin
IL	interleukin
MCP	metacarpophalangeal
MRI	magnetic resonance imaging
MTP	metatarsophalangeal
MTX	methotrexate
NSAIDs	non-steroidal anti-inflammatory drugs
PGA	patient global assessment of disease activity
PIP	proximal interphalangeal
RA	rheumatoid arthritis
RF	rheumatoid factor
SDAI	simplified disease activity index
SJC	swollen joint count

TIT	Tinetti test
TJC	tender joint count
TNF	tumour necrosis factor
TNF-i	tumour necrosis factor inhibitor
TS	tandem stand test
TUG	timed get up and go test
TW	tandem walking test
US	ultrasound
VAS	visual analogue scale

Abstract (English)

Control of disease activity is the crucial factor in treatment of rheumatoid arthritis (RA). Alleviation of acute symptoms as wells as prevention of long-term damages are highly dependent on suppression of inflammatory activity. The two studies of this cumulative thesis investigated relations between disease activity and certain clinical (fall-assessment) and serological (autoantibodies) parameters. The first work could show that RA patients with an increased inflammatory activity have a higher risk to fall. The second study could demonstrate that anti-rheumatic therapy and the consecutive reduction of disease activity is linked with titre changes of the autoantibodies rheumatoid factors and antibodies against cyclic citrullinated peptides. Good treatment response leads to a significant decrease of both antibodies, which have a high diagnostic and also prognostic value in RA. Both studies should contribute current aims of identifying individual risk factors in RA and therefore treating patients to a treatment target.

Abstrakt (German)

Die Kontrolle der Krankheitsaktivität spielt bei der Behandlung der Rheumatoiden Arthritis (RA) die entscheidende Rolle. Sowohl die Milderung akuter Beschwerden, als auch die Vermeidung von Langzeitschäden, hängen in erster Linie von einer Unterdrückung der entzündlichen Aktivität ab. In den beiden hier zu einer kumulativen Dissertation zusammengefassten Arbeiten wurde untersucht, inwieweit die Krankheitsaktivität sich auf konkrete klinische und serologische Parameter auswirkt. In der ersten Arbeit konnten wir zeigen, dass bei an RA Erkrankten ein Zusammenhang zwischen einer erhöhten entzündlichen Aktivität und dem Risiko zu stürzen, besteht. Die zweite Studie demonstrierte die Auswirkungen einer antirheumtatischen Therapie und einer damit verbundenen Senkung der Krankheitsaktivität auf die Autoantikörper Rheumafaktor und Antikörper gegen zyklisch citrullinierte Peptide. Ein gutes Ansprechen auf eine medikamentöse Therapie war mit einer signifikanten Titerreduktion dieser beiden Antikörper, welche sowohl eine diagnostische, als auch eine prognostische Bedeutung haben, verbunden. Beide Studien sind im Kontext aktueller Bestrebungen nach einer personalisierten Medizin mit Identifikation individueller Risikofaktoren und der Behandlung dieser, zu klar definierten Zielen, (“treat to target”) zu sehen.

1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory joint disorder in adults and is characterized by chronic synovitis, systemic inflammation and autoantibody production [1]. Functional disability, cartilage and bone destruction are the major negative outcomes in RA and are related to loss of life quality and to premature death [2-4].

Within the last years the management of RA improved tremendously: Insights into the pathogenesis made the development of a number of new, highly effective drugs possible. These biological agents are targeted against single components of the immune system, which are involved in the inflammatory process of RA. Also traditional disease modifying anti-rheumatic drugs (DMARDs) like methotrexate, leflunomide and sulfasalazine, which were established in the treatment of RA for decades, have been re-examined to improve efficacy. Moreover therapeutic approaches have changed with gain of knowledge: current treatment strategies require an early start of DMARD therapy, a tight control of disease activity to survey treatment response and, if necessary, a rapid switching of therapeutic regimes [5].

Suppressing disease activity is the major goal in RA therapy as uncontrolled activity causes acute symptoms, but also seems to be the main reason for the adverse long-term effects [6].

The aim of the presented papers was to examine the impact of disease activity on clinical and serological parameters. In the first study we investigated how states of disease activity are related to the risk of falling in RA patients. Former works have shown that patients who suffer from RA have an increased risk of falling [7]. In normal populations age and related comorbidities are considered to be major risk factor for falls [8]. Interestingly, in RA the fall incidence seems to be independent from age as well as from disease duration [7, 9]. These findings indicate that different risk factors for falls are relevant in RA, which we tried to identify.

The second study looked at associations between changes of disease activity and changes of rheumatoid factor (RF) and antibodies against cyclic citrullinated peptides (ACPA) levels during a treatment course. RF and ACPA are commonly found in the serum of RA patients and are therefore established diagnostic markers [10]. Furthermore the presence of these auto-antibodies is related to a more aggressive and destructive disease [11]. For this reason changes of RF and ACPA levels can be

highly relevant for the long-term outcome of RA. Both studies can be seen in the context of current efforts of treating RA patients to a treatment target [3] and the intentions of personalized medicine considering individual risk factors [12].

In the following section a brief overlook of the etiopathology, clinical manifestations, diagnosis and treatment options of RA shall be given. Moreover important methods of evaluating disease activity in RA and clinical and serological parameters that have been used in the presented works will be introduced.

2. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most frequent inflammatory arthritis and has a chronic, disabling and aggressive nature. It is related with a twice as high mortality rate [13]. In the industrialized world the prevalence lies between 0.5 – 1% with 5 to 50 per 100.000 new cases each year [1]. Two thirds of the affected patients are women. The disease can appear at any age, with an increase of incidence in elderly people, so that the prevalence in over 65 year olds is between 2-3% [14].

2.1. Aetiology

Aetiology of RA is still unknown. It is suspected that the disease results from a complex interaction between genes and exogenous influences like infections, environmental and hormonal factors [15]. Several genes have been identified to be risk factors for the development of RA and there is a significant overlap with genes associated with other autoimmune diseases, like systemic lupus erythymatodes, ankylosing spondylitis, inflammatory bowel disease and multiple scleroisis [16]. Up to now the strongest genetic associations are found with the human leukocyte antigen major histocompatability genes (HLA). In total it is estimated that genetic factors contribute 50 to 60 percent to the risk of developing RA [17].

The possible role of a viral infection, like Epstein Barr virus, as a trigger of RA in patients with a genetic susceptibility has been discussed for years and remains an active area of investigation [18]. From the known environmental stimuli smoking seems to have the strongest impact on developing RA. Smokers have a 3 times higher risk than non-smokers [19], heavy smoking (41-50 pack years) increases the risk for developing RA 13-fold [20].

2.2. Pathogenesis

Like the aetiology, the pathogenesis of RA remains unclear. In latest opinion RA is considered as a clinical syndrome, which is caused by numerous disease subsets. These subsets lead to different inflammatory cascades, which all end in a common pathway that entail to synovitis and bone and cartilage damage [1, 21]. An unknown environmental trigger causes an activation of T-lymphocytes in genetically vulnerable

individuals. The activated T-lymphocytes interact with B-lymphocytes, which lead to an autoantibody production. Furthermore interactions between activated T-lymphocytes and macrophages cause an overproduction and over-expression of several cytokines including tumour necrosis factor (TNF) alpha, interleukin (IL) 6, IL 1. These cytokines initiate a proliferation of fibroblasts and lead to an invasion of inflammatory cells into the synovial membrane. Fibroblasts are thought to play an important role for the joint destruction through the production of metalloproteinases. Activation of osteoclasts seems to be responsible for the bone erosion [22]. [1, 23]

2.3. Clinical manifestation of RA

RA is characteristically a chronic polyarthritis. At the beginning of the disease the majority of the patients complain about unspecific symptoms like fatigue, weakness, nebulous musculoskeletal pain and loss of weight. This prodrome can last for weeks or even months. Later more specific symptoms like morning stiffness, tenderness and swelling of joints are predominant [23, 24].

Joint manifestations

The clinical manifestation of RA with regard to gravity and pattern of joint involvement is very variable. In almost every patient the joints of the hand are affected. Typically alterations occur in the wrists, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the fingers and interphalangeal joints of the thumbs and the metatarsophalangeal (MTP) joints of the toes, whereas the distal interphalangeal joints (DIP) are usually spared out. Figure 1 shows a typical pattern of joint involvement. Other joints like elbows, shoulders, ankles, and knees are also frequently involved. Typically the arthritis is symmetrical [23, 24].

In the axial skeleton, the cervical spine joints (in contrast to the thoracic and the lumbar vertebrae) are often affected. Initially inflammation may cause stiffness of the neck and pain. Ongoing disease could lead to destruction and instability in the segment C1-C2, which could cause a spinal cord compression and paraplegia [25].

Several joint changes can develop with continuing inflammation and are typical for chronic and established RA. These changes are the result of pathologic processes like weakening and destruction of tendons, tendon sheaths, ligaments; looseness of supporting soft tissue structures, loss of cartilage and imbalance of muscles. In the hand an ulnar deviation of the MCP-joints (“ulnar-drift”), a swan neck deformity

(hyperextension of the PIP-joints and flexion of the DIP-joints), a boutonnière deformity (flexion of the PIP-joints and hyperextension of the DIP-joints) are characteristically. Moreover an atrophy of the dorsal interossei muscles is conspicuous. A compressive neuropathy of the median nerve (carpal tunnel's syndrom) and of the ulnar nerve can be a consequence of inflammatory swelling [23, 24]. In the feet the inflammatory process leads to plantar subluxation of the MTP-joints, hallux valgus and subluxation and lateral deviation of the toes [23, 24, 26]. Recurring effusion in the knee can cause a popliteal (Baker's) cyst [27].

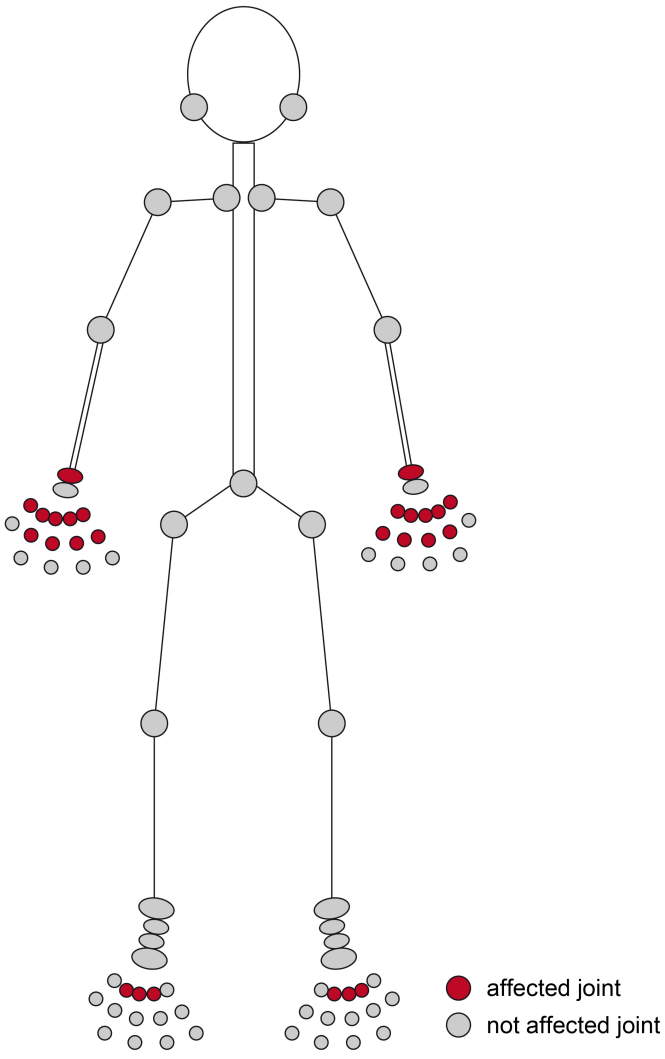

Figure 1: Typical joint involvement. Self-provided.

Extra-artricular manifestations

Extra-artricular manifestations are seen in approximately 40 % of RA patients and in 13 % of the cases these manifestations are considered to be severe [28]. Studies show that smoking and high titres of rheumatoid factor (RF) are risk factors for extra-artricular involvement [29]. Furthermore extra-artricular manifestations are usually associated with a more aggressive disease and premature mortality [30].

Skin involvement: About 20% of RA patients suffer from rheumatoid nodules, which are mostly located in the subcutaneous fatty tissue on pressure points, but can develop in all regions of the body (also in inner organs) [23].

The eyes can be affected in the form of keratoconjunctivitis sicca (common), episcleritis and scleritis. Also uveitis can be seen in RA patients.

Pleuropulmonary manifestations are frequently found in individuals suffering from RA, but seldom cause clinical symptoms. Involvement of the lung includes pleuritis, interstitial fibrosis, pleuropulmonary rheumatoid nodules and pneumonitis [23, 24].

Clinical manifest cardial disorders like pericarditis or endo- and myocarditis are infrequently seen. But several studies have described a significantly increased incidence of cardiovascular disease in patients with RA and it has been shown that premature death in RA patients is frequently related to cardiovascular events [31]. Moreover it seems that the elevated risk for cardiovascular disease is independent of typical risk factors like hypertension, diabetes mellitus, body mass index or hypercholesterinemia [32] [33]. It is suggested that there is an association between the chronic inflammation and atherosclerosis [34, 35].

Generalized osteoporosis is very frequently found in patients suffering from RA. The reasons are immobility, steady treatment effects with glucocorticoids, in the presence of a chronic inflammatory process [23].

RA is also associated with a higher incidence of lymphoma [23, 24, 36].

2.4. Diagnosis

Diagnosis of RA is based on anamnesis, clinical symptoms, laboratory testing and imaging.

Classification criteria

Until recently for clinical studies the 1987 American College of Rheumatology (ACR) classification criteria were used (see Table 1) [37] .

1987 ACR classification criteria for rheumatoid arthritis

At least 4/7 criteria must be satisfied. Criteria 1 through 4 must be present ≥ 6 weeks.

1. Morning stiffness lasting for at least 1 hour
2. Arthritis of 3 or more joint areas
3. Arthritis of hand joints (wrist, MCP, or PIP joint)
4. Symmetric arthritis (same joint areas affected on both sides of the body)
5. Presence of rheumatoid nodules
6. Serumpositivity (Rheumatoid factor)
7. Typical radiographic changes (erosions or unequivocal bony decalcification)

Table 1: 1987 ACR classification criteria [37]

The 1987 classification criteria included criteria points like rheumatoid nodules and typical RA radiographic alterations, which are characteristics of established RA. So the old criteria were not designed for an early diagnosis of RA. But during the last years knowledge of the importance of an early therapeutic intervention for a better clinical long-term outcome grew [38, 39]. In order to identify and study patients in an early disease phase new classification criteria were developed. In 2010 the new ACR/ European League Against Rheumatism (EULAR) classification criteria were introduced [40] (see Table 2).

2010 EULAR/ACR classification criteria of RA

At least 6/10 points are needed for RA classification

A. Joint involvement (Zero to five points)	
One large joint	0
Two to ten large joints	1
One to three small joints (large joints not counted)	2
Four to ten small joints (large joints not counted)	3
More than ten joints (at least on small joint)	5
B. Serology (Zero to three points)	
RF and ACPA negative	0
RF and/or ACPA low positive	2
RF and/or ACPA high positive	3
C. Acute phase reactants (Zero to one point)	
CRP and ESR normal	0
CRP and/or ESR elevated	1
D. Duration of symptoms (Zero to one point)	
Less than 6 weeks	0
6 weeks or more	1

Table 2: 2010 ACR/EULAR classification criteria for RA. RF = rheumatoid factor, ACPA= antibodies against citrullinated proteins, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate [40]

Although the new criteria help to classify patients in an earlier disease stage, it must be kept in mind that there is a difference between classification and diagnosis of RA. Classification criteria serve research and should make minimal mistake on the group level. On the contrary a diagnosis is made to help an individual patient and to enable and facilitate an individual treatment decision [41].

Laboratory findings

Today there is no specific laboratory test for RA. Acute phase reactants like ESR and CRP are often elevated. Both parameters showed good correlation with disease

activity. Furthermore increased values of both acute phase reactants are associated with long-term effects like radiographic erosions [42, 43].

Other typical findings in blood testing are signs of systemic inflammation like a decreased serum iron, thrombocytosis and normocytic anemia.

Several auto-antibodies can be found in RA patients. Between those RF and ACPA are the probably most important. RF is detected in 60 – 80% of patients. But specificity of these antibodies is only modest as they can be also found in other autoimmune-diseases, like systemic lupus erythematosus and primary Sjögren's syndrome. Furthermore increased titres can be found during chronic infections and in older population [10]. ACPA may be more specific (90 to 95%) than RF[44, 45] and have a sensitivity comparable to RF[46] although this is still controversial. Both antibodies are present in the sera of RA up to several years before clinical disease onset [47 48, 49]. Moreover both antibodies also have a prognostic value, since they are associated with more aggressive and destructive disease [11, 50, 51]. RF and ACPA will be discussed more detailed in section 4.

Anti-RA33 is also an antibody with a potential diagnostic value. It is found in approximately 30 % of RA patients [52].

Imaging

The conventional radiography is the most commonly used imaging type in the diagnostics and follow up of RA. Structural alterations like bony erosion, cartilage damage, as well as soft tissue swelling can be detected with conventional radiography [53]. Different scores, like for example the van der Heijde-modified Sharp score, have been developed to quantify radiographic changes [54].

Magnetic resonance imaging (MRI) is more sensitive in detecting bone erosions than plain radiography. Moreover with MRI it is possible to assess disease activity by detecting such as synovitis, tendosynovitis and bone marrow oedema [53].

Ultrasound (US) is able to evaluate soft tissue structures and is useful in detection of synovitis in inflamed joints, (Baker) cysts and appraisal of tendons [53].

2.5. Therapy

The aim of the management of RA is to supress the systemic inflammation and to prevent bad long-term outcome, which leads to impairment of quality of life and invalidity. An early, effective and consequent therapeutic approach is necessary.

The treatment of RA is based upon several pillars: On the one hand upon drug treatment, which includes 1. analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), 2. traditional disease modifying anti-rheumatic drugs (DMARDs), 3. biologicals and 4. glucocorticoids and on the other hand upon non-medicamentous therapy like physiotherapy, occupational therapy and psychological support and surgical procedures [5].

NSAIDs and analgesics

These medications are the basis for treating symptoms like pain of RA, and are widely used. NSAIDs additionally have a positive effect on inflammation. It must be pointed out that both medications have no positive influence on the long-term outcome of the disease [23]. Moreover gastrointestinal and cardiac adverse effects must be kept in mind [55, 56].

DMARDs

DMARDs are a heterogeneous group of medicaments, which are able to reduce disease activity and have a positive influence on the disease course in regard to preserving joint function and preventing joint destruction. Although the mechanisms of the immune modulation are still not fully understood, they are the mainstay of the treatment of RA. Methotrexate (MTX) is the first line DMARD in the absence of contraindications. If there are contraindications against MTX, leflunomide or sulfasalazin can be prescribed [5]. Gold, azathioprin and ciclosporin are nowadays only rarely used because of their toxic side effects [23].

Biologicals

Research on inflammatory and pathological processes in RA during the last couple of years allowed the identification and blockade of pro-inflammatory cytokines and so enabled new therapeutic approaches. Up to four different highly effective classes of biological agents are used in the treatment of RA. Inhibition of the tumour necrosis factor (TNF α) was the first licensed biological mode of action. Currently five TNF-inhibitors (TNF-i) are approved: infliximab, adalimumab, etanercept, certolizumab and golimumab. Other modes of action are co-stimulation of T-cells inhibition (abatacept), blockade of interleukin- (IL-) 6 (tocilizumab) and B-cell depletion

(rituximab) [1, 57]. IL-1 inhibition (anakinra), another treatment strategy, could not match the efficiency with the previously mentioned biologicals [58]. Usually biologicals are combined with traditional DMARDs, typically MTX [5].

Glucocorticoids

Glucocorticoids have been used in the therapy of RA for decades. They are able to rapidly reduce disease activity and have the potential to improve the long-term outcome of RA, but also cause adverse effects like infections and osteoporosis. In current treatment strategies they are used for bridging the gap between the start of a new DMARD course and the time point of onset of its clinical effectiveness, and during flare-ups of disease activity [59]. Furthermore intra-articular injections of corticosteroids in active joints showed high efficacy [60].

3. Disease activity in RA

The standardised evaluation of disease activity is of central importance for the management of RA. As heightened disease activity over prolonged time leads to joint destruction and functional impairment, the surveillance of activity is an important goal in the therapy of RA [61, 62]. Several instruments and clinical indicators for disease activity and clinical response criteria have been developed for the assessment of RA. They are used in the context of clinical studies, but more and more also in clinical practice [63]. A number of important individual variables as well as composite indices will be described in the following section.

3.1. Core sets of disease activity variables

In the early 1990s different groups of researchers published core sets of disease activity variables, which should be used in the assessment of RA in clinical trials [64-66]. These variables included swollen and tender joint count (SJC, TJC), pain evaluation through the patient, patient global assessment of disease activity (PGA), evaluator global assessment of disease activity (EGA) and evaluation of acute phase reaction and function. The selection of these variables was based on clinical data and rested upon various aspects of validity [62].

Pain

Pain is the leading symptom in RA. Usually it is measured on a 100 mm visual analogue scale (VAS) [67, 68]. On this scale patients mark their extent of pain during the last week between 0 mm (no pain) and 100 mm (worst imaginable pain). Other instruments to measure pain are also available and reliable [69, 70]

Tender Joint Count (TJC) and Swollen Joint Count (SJC)

In RA patients, joints are usually evaluated for tenderness on pressure (TJC) and swelling and effusion (SJC). The first joint count was introduced in 1950s and included 86 joints [71]. Until the late 1980s the number of evaluated joints was gradually reduced and actually the assessment of 28 joints is mainly used in clinical studies as well as in daily practice [72, 73 74]. The 28 joint count includes the following joints: 10 PIP joints of the fingers, 10 MCP joints, the wrists, elbows, shoulders, and knees. Although the measurement with the reduced number of joints does not include the assessment of feet and ankles, it showed a good validity and reliability in

clinical studies [75, 76] [70]. Moreover the 28 joint count is part of the composite indices disease activity score 28 (DAS-28) [77], simplified disease activity index (SDAI) [78] and clinical disease activity index (CDAI)[79].

Patient global assessment (PGA) and evaluator global assessment (EGA)

For the rating of global disease activity through the patient (PGA) and the physician (EGA) are also mainly 100 mm visual analogue scales used. The PGA is regarded as a subjective parameter, while the EGA is considered as a combination of subjective and objective. Usually the PGA is rated higher than the EGA [62]. A recent study showed that rating of the PGA is mainly pain driven, while the EGA is closely linked to SJC [80].

Acute phase reactants

The most commonly used acute phase reactants are CRP and ESR. They are employed in clinical practice as well as in clinical trials. Both parameters showed good correlations with disease activity and also with radiologic progression [42, 81]. CRP may be superior to ESR in regard of measuring disease activity [82].

3.2. Composite indices

RA is a very heterogeneous disease, which makes assessment of disease activity more complex than in other diseases. A single parameter can hardly reflect the different aspects and characteristics that can indicate disease activity. In order to homogenize the evaluation of disease activity several composite indices have been developed [83]. Primarily they were meant for report of disease activity and to measure therapy response in clinical studies, but nowadays they are also recommended for daily clinical practice [62]. In the following section three commonly used composite indices, which were also used in the here presented papers, are going to be presented: **d**isease **a**ctivity **s**core 28 (DAS-28), the **s**implified **d**isease **a**ctivity **i**ndex (SDAI) and the **c**linical **d**isease **a**ctivity **i**ndex (CDAI). The formulas to calculate the three indices are given in table 3.

Disease activity score 28 (DAS-28)

The original DAS was introduced in the early 1990s by van der Heijde et al. and employed the Ritchie articular index and a 44 joint count [84]. A few years later the DAS was successfully modified and the DAS-28 was introduced, which is based on a more practicable 28 joint count (TJC and SJC). Other included variables are PGA

and ESR [77]. There also exists a variant using CRP instead of ESR (DAS-28 CRP) [85]. The formula to calculate the DAS-28 remains very complex and requires a calculator. Four cut-points have been established which divide disease activity into remission (< 2,6), low disease activity (≥ 2,6 and < 3,2), moderate disease activity (≥ 3,2 and < 5,1) and high disease activity (≥ 5,1) (See also table 3). Given the complexity of DAS-28 calculation, the idea to generate a more simple disease activity score came up and in 2003 the SDAI was introduced [78].

SDAI and CDAI

The SDAI is calculated by adding the values of the core set variables SJC, TJC, PGA, EGA and CRP (table 3). So the used variables were neither weighted nor transformed. Despite the simplicity the SDAI showed very good correlations with the DAS-28 and with measures of functional impairment (health assessment questionnaire). Furthermore it was well associated with radiographic progression. Cut off levels for remission and other states of disease activity have been postulated and the SDAI was validated in several trials [86-88].

In 2005 Aletaha et al. could show that acute phase reactants (CRP) in composite indices only provide little additional information to the clinical core set parameters. The CDAI was developed, which is only based on SJC, TJC, PGA and EGA and calculated by adding these parameters. It was the first composite index requiring no blood testing, thus allowing immediate evaluation, making it very practicable for clinical use. The CDAI has also been validated and showed good correlations with other disease activity indices (DAS-28 and SDAI), as well as with function and radiographic progression over time [79].

DAS-28
Formula: 0,56 x √(TJC 28) + 0,28 x √(SJC 28) + 0,70 x lognat(ESR) + 0,014 x PGA
Cut-off values: remission: < 2,6 low: ≥ 2,6 and < 3,2 moderate: ≥ 3,2 and < 5,1 high: ≥ 5,1
SDAI
Formula: SJC 28 + TJC 28 + PGA + EGA + CRP
Cut-off values: remission: ≤ 3,3 low: > 3,3 and ≤ 11 moderate: > 11 and ≤ 26 high: > 26
CDAI
Formula: SJC 28 + TJC 28 + PGA + EGA
Cut-off values: remission: ≤ 2,8 low: 2,8 and ≤ 10 moderate: > 10 and ≤ 22 high: > 22

Table 3: Formulae to calculate composite indices: DAS-28, SDAI and CDAI. SJC: swollen joint count, TJC: tender joint count , PGA: patient global assessment on VAS in cm, EGA: evaluator global assessment on VAS in cm. CRP: c-reactive protein in mg/l. Adopted from [89].

3.3. Assessments for physical functioning

The most important instrument to measure physical function is the **health assessment questionnaire (HAQ)**, which was introduced in the 1980s [90]. It consists of questions concerning five dimensions: disability, costs, pain, adverse effects of medication, and mortality**.** In rheumatology only the HAQ disability index (HAQ-DI) is widely used. It measures the ability to manage daily life activities. In total it contains 20 questions, which are divided in 8 categories: dressing, eating, reaching, rising, walking, hygiene, grip and usual activities. Patients answer each question on a four level scale, which ranges from 0 (no difficulty) 1 (some difficulty), 2 (much difficulty) and 3 (unable). The result of the HAQ-DI is the mean of the highest values of each category. So the final score ranges between 0 and 3. A score under 0.3 is considered as normal [91]. The HAQ-DI is highly influenced by disease activity, but also increases consistently with disease duration and joint destruction [92 93 94].

3.4. Response criteria

Response criteria have been developed to evaluate drug effects in clinical studies. The first response criteria were the **Paulus response criteria**, which have been published in 1990 [95]. Based on these criteria the **ACR response criteria** were introduced a few years later, which since then have been used widely in clinical RA trials since then [96]. The ACR criteria are defined as a 20% improvement in SJC and TJC as well as a 20% improvement in three of the five ACR core set variables: PGA, EGA, pain, disability and an acute phase reactant. The ACR 20% allow certain discrimination between active drug therapy and placebo [62]. As therapy options in RA improved, a bettering of 20% was considered as low and so the ACR response criteria were extended by ACR 50% and ACR 70%, to mark more substantial improvement [97].

In contrast to the dichotomous ACR 20, 50 and 70 criteria, the **ACR numeric percentage criteria (ACR-n)** allow a relative evaluation of treatment response. ACR-n is defined as the smallest relative response of SJC, TJC and the median of the other five ACR core set variables [98]. This response measurement is controversial [99, 100, 70].

The **EULAR response criteria**, which were introduced in 1996, are based on the DAS-28 and distinguish between non-responders, moderate responders and good responders. Moderate response is achieved when DAS-28 decreases by more than 1.2, but does not reach low disease activity, or by a DAS-28 decrease between 0.6 and 1.2 points and reaching at least moderate disease activity. Good response is reached when DAS-28 declines by ≥ 1.2 and low disease activity is achieved. So in the EULAR response criteria not only the change in disease activity is important, but also the reached state of disease activity [101, 102].

In 2012 treatment **response criteria** based on the **SDAI** and **CDAI** were published. These criteria are graded into mild, moderate and major treatment response. Cut-off levels have been chosen in a way that they correspond to the ACR response criteria. A relative change of 50% of the SDAI (SDAI 50%) corresponds to ACR 20%, SDAI 70% to ACR 50% and SDAI 85% to ACR 70% [103].

4. Study variables

In the following section the parameters, which have been examined in the presented papers shall be introduced. On the one hand the serological parameters rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA), which are established markers in the diagnostic approach to RA and whose characteristics during anti-rheumatic therapy and changes of disease activity have been studied. On the other side the effects of disease activity on clinical parameters/tests, which predict the risk of fall, like Chair-Rising Test (CRT), Timed Get Up And Go Test (TUG), Tinetti Test (TIT), Tandem Stand (TS) and Tandem Walking (TW) Test.

4.1. Rheumatoid factor

RF are antibodies directed against the Fc fragment of immunoglobulin G (IgG) and were first described 1940 by Waaler. In RA these auto-antibodies are produced by B-cells that are located in lymphoid follicles and in germinal center-like structures, which develop in inflamed joints [10]. IgM is the predominant isotype. Determination of RF levels determination is possible with nephelometry, enzyme linked immunosorbent assay (ELISA) and also older methods like Waaler-Rose haemagglutination and latex agglutination. ELISA also allows a detection of subtypes like RF IgG and IgA, while nephelometry mainly and Waaler-Rose and late agglutination only measure IgM titres [104].

RF is detected in 60 – 80% of RA patients. But the diagnostic usability is limited, because, as mentioned before, RF can also be found in a number of other diseases, especially during infections and other autoimmune-diseases [10]. Moreover RF can be detected in 5 % of general population and up to 10 % in elderly [24]. Furthermore about 30 % of RA patients are seronegative for RF. Although RF levels can be increased years before disease onset [48], RF might only be measured in 50% of patients in early phase of RA [105]. Though several studies could show that RF levels > 50 IU/ml and the presence of RF IgA subtypes are relatively specific for RA [106] [10, 107].

Beside the diagnostic value, RF also has a prognostic relevance. Several studies could show that seropositivity for RF is associated with a more aggressive disease, with stronger radiographic progression and the occurrence of extra-articular manifestations [11, 28, 108-110]. For example are elevated RF levels the strongest

predictor for the development of rheumatoid vasculitis [111]. Rheumatoid nodules are in almost every case associated with RF seropositivity [23].

4.2. Antibodies against citrullinated peptides

The second types of autoantibodies, which are commonly used in clinical practice, are antibodies against citrullinated peptides (ACPA). This group of antibodies reacts with epitopes in which arginine is converted by the enzyme peptidylarginine deiminase into citrulline [11]. Up to now keratin, vimentin, fibrin and alpha enolase have been identified as citrullinated antigenes [112]. Like RF, ACPA are locally produced by B-lymphocytes in inflamed joints, where citrullination of proteins during inflammatory processes takes place [10, 113]. For detection of ACPA, assays using cyclic citrullinated peptides (CCP) were developed, which are easier to produce and to standardize than linear stretches of citrullinated peptides [44, 51]. These anti-CCP assays were the first commercial available tests for ACPA. Advancements of the original anti-CCP assays are now in use (second generation anti-CCP), which showed an increased sensitivity and specificity [114].

ACPA are detected in 64 to 89% of RA patients, depending on the study population, and are highly specific (88 to 99%) for RA [51, 115]. It is often seen that RA patients are seropositive for both RF and ACPA. If RF and ACPA are present, the specificity to predict RA is almost 100% [51].

Increased ACPA levels can also be detected in other autoimmune diseases like systemic lupus erythematosous (SLE), Sjögren's syndrome and myositis, usually associated with erosive joint involvement [112]. Moreover a study showed that ACPA can be present in the serum of patients with active tuberculosis [116]. Interestingly, also an association between previous or ongoing cigarette smoking and elevated ACPA levels was described [51].

ACPA can be found in RA patients several years before disease onset. In a study testing ACPA and RF serum levels of RA patients who had been blood donors before disease onset, auto-antibodies could have be found on average 4.5 years before RA symptoms occurred [48].

Like RF the presence of ACPA is also associated with an aggressive course of disease. Studies described that increased ACPA levels in early RA lead to more joint erosions [117-119]. Moreover ACPA seropositivity and elevated levels are related with higher CRP and DAS-28 values [120]. Although ACPA and RF are associated with radiographic progression, it has been shown that they are independent risk factors [11].

4.3. Clinical parameters: Tests of the fall assessment

In the presented paper “Rheumatoid arthritis and falls: the influence of disease activity” five tests were used to evaluate the risk of falling: the Chair-Rising Test, Tinetti Test, Timed Get Up and Go-Test, Tandem Walk and Tandem Stand-Test [121].

In the **Chair-Rising Test** (CRT) [122] a patient is asked to stand up and sit from chair down five times in a row as quickly as possible. The participant is not allowed to use his arms. Time is measured. This test checks in first line muscle strength and the risk of falling is elevated if a patient needs more than 10 seconds to complete the test or is not able to accomplish the exercise [123].

The **Tinetti Test** (TIT) or also named Performance Oriented Mobility Assessment (POMA) is a widely used tool to assess the risk of falling in elderly [124], but also in patient collectives with neurological diseases like Huntigton’s and Parkinson’s disease or individuals who have suffered a stroke [125-127]. It was developed in the 1986 and consists of two parts: a balance test and gait test. A maximum of 28 points can be achieved. Values of 23 or lower are associated with an increased risk of falling.

The **Timed Get Up and Go Test** (TUG), which was introduced in the early 1990s measures muscle strength, gait speed and balance [128]. At the beginning of the test the participant is seated on a normal height armchair and has his hands on the armrests. Time is measured while the person rises, walks 3 meters at his normal gait speed, turns around, returns back to the chair and sits down again. The more time is needed to complete the test, the more restricted is his mobility. The TUG is an simple and effective method to assess functional mobility by simulating an every day life setting [129]. Several geriatric societies recommend this test to identify patients with an increased risk to fall [130].

The **Tandem Stand** (TS) and the **Tandem Walk** (TW) are both tests, which evaluate balance capacity [122, 131]. In the TS it is tested how long a participant can hold a given position, without losing his balance. First the patient is asked to stand in side-by-side position for ten seconds. If he is able to do so, the next checked position is the semi-tandem stand for ten seconds (the heel of one foot is placed on the side of the first toe of the other foot). At last the full-tandem stand (both feet are directly in line) is examined for 10 seconds. The longer the given position can be hold the better is the test performance. The TS has been used in several studies [129].

At the TW test an individual is requested to walk heel on toe on a 2 meter long and 5 cm broad line. The false steps are counted. Like the TS, the TW was related with recurrent falls [132]. [121]

5. Aims of the studies

The aims of the presented studies were to analyse the impact of disease activity on clinical and serological parameters. Both studies should be seen in the context of the current efforts of treating RA patients to a treatment target [3] and the intentions of personalized medicine considering individual risk factors [12].

One still underestimated but highly relevant risk in patients with RA is the risk of falling. It was our objective to examine the relation between the risk of falling in RA patients and disease activity. Therefore we recruited 78 patients in the outpatient clinic of the Department for Rheumatology at the General Hospital of Vienna. First the patients were asked to complete a questionnaire about falls during the last 12 months; fear of falling; disease duration and possible risk factors that might be associated with an increased danger of falling. Later disease activity was assed. The following parameters were measured: the core set variables SJC, TJC, PGA, EGA CRP, ESR. Moreover we determined ACPA, RF, pain (on a VAS), HAQ-DI and the composite indices SDAI, CDAI and DAS-28. The risk of falling was evaluated with a fall assessment consisting of the five tests mentioned above: TIT, CRT, TUG, TS and TW. For statistic analysis we correlated each disease activity parameter with the tests of the fall assessment. Furthermore we compared the fall assessment results across the disease activity states (remission, low activity and higher activity).

High titres of RF and the presence of ACPA are associated with a more severe and destructive disease. Therefore changes in the titres levels can be therapeutically highly relevant. In the second study it was our objective to examine changes of ACPA and RF levels during the course of anti-rheumatic treatments. Hence we obtained data of patients who were seen at our outpatient clinic and which started a traditional or biological DMARD therapy course. We calculated changes of ACPA and RF levels as well as disease activity parameters between the baseline visit and after 3, 6, 12 and 18 months. Next we looked at differences in ACPA/RF levels between treatment responders and non-responders due to SDAI 50% response criteria. Moreover we correlated changes of disease activity parameters and changes of ACPA/RF levels. Furthermore we examined effects of disease duration, type of therapy and the trend over 18 months.

6. Discussion

In 2010 an international expert group published a guideline for treating RA to a target. This committee presented four overarching principles and ten recommendations for the management of RA. Beside recommendations concerning treatment goals, intervals of clinical visits and measurements of disease activity one recommendation also included taking individual patient-related factors into account [3]. Moreover in the last years the concept of personalized medicine got more and more established in RA and the identification of individual risk factors has gained importance in treatment strategies. In the presented studies we examined two individual or patient related risk factors and their relation to the state and changes of disease activity, respectively.

The first study dealt with the risk of falling in RA patients and how the risk to fall is associated with disease activity. Falls have a tremendous impact on public health and are one of the main health care concerns in elderly society. Beside mild injuries like abrasions and lacerations, in 10% of the cases fractures occur [133]. This results in an increased morbidity and mortality [134, 135]. Furthermore falls and the consequences of falls have high economic relevance: only in the USA the direct and indirect annual costs of falls range between 75 and 100 billion dollars [136]. [89]

Former studies on the topic falls and RA in first line investigated the prevalence of falls. They found an increased prevalence of falls, with rates ranging from 33% to 54% per year [7, 9, 137-141]. Some risk factors have been described in the quoted studies, but we are not aware of a work, which could demonstrate a systematic relation between disease activity and risk of falling. All three of the composite disease activity indices (SDAI, CDAI and DAS-28) showed significant correlations to tests of the fall assessment and we could show that patients with higher levels of disease activity are in greater risk to fall. The strongest association of the collected parameters was found with the HAQ-DI. The HAQ-DI has also been identified in former studies as a risk factor for falls. These results are insofar not surprising as the HAQ-DI is a parameter for physical function. We ascribed the strong correlation to the fact that the HAQ-DI is influenced by reversible as well as irreversible components [94]. The reversible component is the stage of disease activity: Studies demonstrated that the HAQ-DI rises with higher disease activity and falls in remission or lower activity [142]. Furthermore disease activity was identified to be the strongest

influencing factor for the HAQ-DI at all stages of disease duration [92]. Contrariwise with on going disease duration the impact of RA activity on the HAQ-DI decreases and the reversibility of HAQ-DI in lower stages of disease activity diminishes. On going joint destruction, musculoskeletal consequential damages and coexisting conditions, which limit physical function, are discussed to be responsible. These are the irreversible components, which influence the HAQ-DI. So it could be possible that the risk of falling in RA patients is also influenced by reversible components (disease activity) as well as irreversible components (long-term damages) [94]. [89]

Other activity parameters, which highly correlated to the fall assessment results, were TJC, PGA and pain. These parameters have in common that they are patient reported outcomes, whereas more objective disease activity parameters like SJC, EGA, acute phase reactants (ESR and CRP) and the specific auto-antibodies (RF and ACPA) showed no significant relation to the risk of falling. This underlines the importance of patient reported outcomes and is an useful expansion of their application in measuring disease activity of RA. Moreover the fact, that mainly patient-derived disease activity parameters reflect the risk of falling, confirms the intentions of a “shared decision making” between physician and patient [3, 143].

Of the core set parameters, which were related to the fall risk, pain seems to be the crucial factor [89]: A recent study showed that pain is the sole paramount determinant for patient’s valuation of disease activity [80]. Furthermore former works could demonstrate that chronic musculoskeletal pain is associated with an increased risk of falling [144] and that pain is most important factor for physical impairment in early stage of disease [145].

Beside the patient reported outcomes all used composite disease activity scores (DAS-28, SDAI and CDAI), which include patient as well as evaluator and laboratory based RA activity parameters, showed strong correlations to the results of the fall assessment. This confirms the relevance of composite indices in the complex measurement of disease activity in RA and their value in assessing outcomes [63]. Nevertheless we found the strongest association to the CDAI, which in contrast to DAS-28 and SDAI does not include an acute phase reactant component.

Our results imply further research. A study design where the risk to fall is assessed in patients several times during a treatment course and so at different stages of disease activity, could help to gain deeper insights into relations between RA activity and risk of falling and possibly also information about the responsible pathological

mechanisms. Moreover radiological changes and their influence on the risk of falling should be examined.

The parameters, which are highly related to the risk of falling, can all be easily obtained and do not afford laborious examination. Furthermore they are mainly part of an international committee recommended measurement of disease activity [3]. It also takes only a few minutes to accomplish the here used tests of the fall assessment. So in order to prevent falls in RA, in patients with pain or increased disease activity risk to fall should be evaluated and patients should consult additional physiotherapeutic and occupational support if needed.

In the second study we examined how ACPA and RF levels react in RA patients during an anti-rheumatic treatment course and analysed how far changes of the AAB titres are linked with changes in disease activity. Furthermore we assessed differences between changes in these antibody systems and also investigated potential influential factors like treatment response, disease chronicity, or type of treatment.

ACPA and RF are both linked with radiologic progression [117, 146] as well as with a more aggressive disease course [50, 51] and RF with the extra-articular disease manifestations [11]. Therefore decreases in their levels may be highly relevant to improve the long-term outcome of RA.

In the presented study we could demonstrate that RF and ACPA levels decrease significantly after 6 months of treatment. These findings are in line with smaller previous studies, which mainly examined changes under individual TNFi [147-149]. In our analyses RF appears to be more reactive than ACPA, as we found significantly higher declines (absolute and relative) and a larger number of patients who improved with RF levels compared to ACPA levels. The smaller decreases of ACPA levels might explain discrepant views on changes of ACPA, which have been reported, and why some authors even described no decrease of ACPA levels during therapy[150-152].

A reduction of both types of AAB went alongside a fall in disease activity, but treatment responders, in the current study defined as patients with a SDAI50 response, had significantly higher ACPA and RF declines than non-responders.

Previous studies using the ACR response criteria found similar results [147, 148]. Furthermore we could show that chances to have a reduction of AAB levels grow with achieving better treatment response (ACR and SDAI criteria).

An interesting result was that in non-responders ACPA levels did not decline significantly, whereas RF levels still did. This might be a consequence of the different isotypes of these two AABs: RF, as measured here, belong to the IgM immunoglobulin class and may be mostly produced by B-1 B-cells, whereas ACPA, as measured by ELISA, are of the IgG class which may show less rapid responsiveness to therapeutic interventions. Other explanations could be that anti-rheumatic drugs specifically influence RF production or that RF level decreases are a sign of a subclinical therapeutic effect.

When we correlated changes of single disease activity parameters with changes of ACPA and RF levels, we found significant relations between both AAB and the acute phase reactants CRP and ESR. RF changes also correlated with SJC, pain and PGA. We could only speculate about theses relations: RF may be more strongly involved in activating cytokine production within the joints and these local events are linked with swelling and pain.

In our cohort RF level declines were significantly higher in patients with a disease onset of less than 12 months; in 94% of the study participants with early RA RF levels improved. In accordance with the bad prognostic impact of these particular antibodies, this could indicate the long-term outcome can be influenced only at an early stage of the disease in a large number of patients, consistent with the “window of opportunity” theory in RA[39, 153, 154]. In contrast, in our cohort changes of ACPA were not influenced by disease duration.

We did not find any treatment type that had a specific impact on the changes observed in the AAB levels; indeed, after adjustment for disease activity all differences between the treatment groups disappeared.

When we looked at the trend over 18 months we found that SDAI decreased fastest and remained stable after 6 months of therapy. RF and ACPA declined consistently and both reached the lowest level at the endpoint of this defined period, but RF levels decreased considerably faster than ACPA levels. Again, differences in the immunoglobuline (Ig) class might be an explanation for these differences [10].

Additional research is required to examine the impact of ACPA and RF level declines for the long-term outcome of RA patients. A study, which compares functional and structural outcomes of two cohorts: One cohort includes patients, whose RF and/or ACPA levels could be significantly reduced during a treatment course and the second

includes patients, whose AAB levels remained unaffected. This design could help to understand the prognostic benefit of an AAB levels reduction.

In the two presented studies we could show that the risk to fall in RA patients as well as changes of RF and ACPA levels are related with state or changes of disease activity. Furthermore we could identify single parameters, which are related with a higher risk to fall and which correlated to changes of the AAB levels.

In the last two decades the therapeutic opportunities in individuals with RA made tremendous progress. This progress is not only based on the development of new, highly effective drugs, but also on the introduction of structured guidelines for the management of RA [5], the definition of strict treatment goals and the development of validate outcome measures [3, 155]. In addition, like in other fields of medicine, the intentions for personalized medicine and individualized treatment strategies grew. One way to support these aims is to focus research on markers, which can predict treatment response. In the last year several studies were conducted with the aim to identify predictors of response [156]. Another concept to further individualized medicine is the identification of individual risk factors, which have influence on the long-term outcome of RA or which are able to predict adverse events. The current studies can be seen in the latter context.

At the same time the results of both works confirm the importance of controlling disease activity, as a reduction of RA activity is also linked with a reduction of the risk to fall and a decrease RF and ACPA levels and so adverse events can be avoided and the long-term outcome can be improved.

7. References

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9. Article summaries

9.1. Rheumatoid arthritis and falls: the influence of disease activity

Christoph Böhler, Helga Radner, Michaela Ernst, Alexa Binder, Tanja Stamm, Daniel Aletaha, Josef S Smolen and Marcus Köller

Rheumatology 2012;51:2051-2057

Objectives: To examine the correlation between the disease activity of rheumatoid arthritis (RA) and the risk of falling.

Methods: 78 patients were tested. Disease activity was measured with acute phase reactants, autoantibodies, swollen and tender joint count (SJC28, TJC28), pain on a visual analogue scale (VAS-pain), patient and evaluator global assessment of disease activity (PGA, EGA), Health Assessment Questionnaire Disease Index (HAQ-DI), Disease Activity Score - 28 (DAS-28), Clinical and Simple Disease Activity Index (CDAI, SDAI). The risk of falling was evaluated by a fall assessment consisting of Tinetti Test (TIT), Timed Get Up & Go-Test (TUG), Chair-Rising Test (CRT), Tandem Walk (TW) and Tandem Stand-Test (TS).

Results: 26.9% of the participants reported a fall during the last 12 months, 46.2% mentioned the fear of falling. The most evident link (Spearman Correlation [r_s]) with the results of the fall assessment was found in HAQ-DI (CRT: r_s=0.523, TUG: r_s=0.620, TIT: r_s=-0.676), CDAI (CRT: r_s=0.460, TUG: r_s=0.504, TIT: r_s=-0.472), VAS-pain (CRT: r_s=0.441, TUG: r_s=0.616, TIT: r_s=-0.548), PGA (CRT: r_s=0.473, TUG: r_s=0.577, TIT: r_s=-0.520) and TJC (CRT: r_s=0.488, TUG: r_s=0.394, TIT: r_s=-0.385). Patients with higher disease activity achieved poorer results in the fall assessment.

Conclusion: The strongest relation with falls was evident for patient reported outcomes. Pain seems to be the common ground of these parameters. At the same time the disease activity influences pain.

The results suggest an increased attention towards the risk of falling with patients of higher levels of disease activity or pain, and physio- or ergotherapeutical interventions as needed.

The author was leading patient examination, data analysis and drafting of the manuscript.

9.2. Serological changes in the course of traditional and biological disease modifying therapy of rheumatoid arthritis

Christoph Böhler, Helga Radner, Josef S Smolen and Daniel Aletaha

Ann Rheum Dis 2013 72: 241-244

Objective: To investigate changes of rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) during therapy with disease modifying anti-rheumatic drugs (DMARDs).

Methods: We obtained clinical and serological data of patients treated with traditional and biological DMARDs from the treatment start and after 6 months of therapy. With non-parametric tests we analysed changes of ACPA and RF levels between the two visits and the influence of treatment response due to SDAI criteria. Furthermore we analysed potential influential factors as disease chronicity, different therapeutics and the trend over 18 months.

Results: 143 ACPA and RF positive patients were included. The median (25^{th} /75^{th} percentile) relative changes after six months were -35.6% (-63.3; -8.3) for RF, and -15.2% (-40.0; 10.0) for ACPA ($p<0.001$ for both). Changes of RF levels were significantly greater than those seen for ACPA ($p<0.001$). The decrease of ACPA and RF was significantly higher in patients with treatment response than in those without ($p=0.034$ and $p=0.01$, respectively). After adjusting for disease activity only a short disease duration showed an influence on changes of RF levels ($p=0.087$). After 3 months ACPA declined about 4.6% in relation to baseline, RF about 13.2% and SDAI about 23.5%; after 12 months these values were 16.9%, 31.4% 40.5%; and after 18 months 23.8%, 35.2% and 44.3%, respectively.

Conclusion: ACPA and RF levels decreased significantly after 6 months of therapy. Reductions of both AAB were closely linked to a reduction of disease activity. RF declined faster, to a larger extent and in greater numbers of patients than ACPA.

The author was leading study design, data acquisition, data analysis and manuscript drafting.

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Original article

Rheumatoid arthritis and falls: the influence of disease activity

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Abstract

Objective. To examine the correlation between disease activity of RA and the risk of falling.

Methods. Seventy-eight patients were tested. Disease activity was measured with acute-phase reactants, autoantibodies, swollen and tender joint count (SJC28, TJC28), pain on a visual analogue scale (VAS pain), patient and evaluator global assessment of disease activity (PGA, EGA), HAQ disability index (HAQ-DI), 28-joint DAS (DAS-28) and the clinical and simple disease activity indexes (CDAI, SDAI). The risk of falling was evaluated by a fall assessment consisting of Tinetti test (TIT), timed get up and go test (TUG), chair-rising test (CRT), tandem walk and tandem stand test.

Results. During the last 12 months, 26.9% of the participants reported a fall and 46.2% mentioned the fear of falling. The most evident link [Spearman's correlation (r_s)] with the results of the fall assessment was found in HAQ-DI (CRT: $r_s = 0.523$, TUG: $r_s = 0.620$, TIT: $r_s = -0.676$), CDAI (CRT: $r_s = 0.460$, TUG: $r_s = 0.504$, TIT: $r_s = -0.472$), VAS pain (CRT: $r_s = 0.441$, TUG: $r_s = 0.616$, TIT: $r_s = -0.548$) PGA (CRT: $r_s = 0.473$, TUG: $r_s = 0.577$, TIT: $r_s = -0.520$) and TJC (CRT: $r_s = 0.488$, TUG: $r_s = 0.394$, TIT: $r_s = -0.385$). Patients with higher disease activity achieved poorer results in the fall assessment.

Conclusion. The strongest correlation with falls was evident for patient-reported outcomes. Pain seems to be the common ground of these parameters. At the same time, disease activity influences pain. The results suggest an increased attention towards the risk of falling with patients of higher levels of disease activity or pain, and physio- or ergotherapeutical interventions as needed.

Key words: RA, falls, disease activity, patient-reported outcomes.

Introduction

Falls are a common event in patients with RA. Previous studies found a fall incidence within 1 year between 33% and 54% [1–7]. About 68% of patients with RA have an increased risk of falling [5]. In 80% of those who fall injuries ensue [4]. Despite the commonness and the often serious consequences, falls are still an underestimated and poorly researched issue of RA [7]. For the normal population, age and related comorbidities are considered to be the most important risk factor for falls [8]. Surprisingly, the fall frequency in RA patients appears to be age independent [1]. Also, disease duration does not seem to play a role [3]. Until now only a few studies have been performed on the topic of falls and RA, and these have resulted in the identification of several risk factors. However, we are not aware of studies that primarily investigated the influence of disease activity on falls in RA.

Our aim was to examine the relationship between the inflammatory activity of RA and the risk of falling, and to identify those disease activity variables that are risk factors for falling. Moreover, we determined the fall frequency within the previous 12 months and the fear of falling.

Patients and methods

Patients

All patients had RA according to the 1987 classification criteria of the ACR. Patients were recruited consecutively while attending the outpatient clinic of our department. At the beginning, participants were asked to complete

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an interviewer-assisted questionnaire about (i) falls during the last 12 months; (ii) fear of falling; (iii) disease duration; (iv) confounders like hypertension, diabetes mellitus, stroke, atrial fibrillation, polyneuropathy, osteoporosis, joint replacement, vision impairment; (v) other morbidities; and (vi) walking aids. We also obtained the HAQ disability index (HAQ-DI). The ethics committee of the Medical University of Vienna (approval no. 279/2009) approved this study, which was performed at the Department of Rheumatology at the Vienna General Hospital. Subjects' written consent was obtained according to the Declaration of Helsinki.

Disease activity

The following core set variables were evaluated: ESR (mm/h), CRP (mg/dl), swollen joint counts (SJC28), tender joint counts (TJC28), patient global assessment of disease activity [PGA; visual analogue scale (VAS) 0–10 cm], evaluator global assessment of disease activity (EGA; VAS 0–10 cm) and patient's pain assessment (VAS pain 0–10 cm). Composite measures of disease activity, namely the Clinical Disease Activity Index (CDAI), the Simplified Disease Activity Index (SDAI) and the DAS-28 were calculated using the respective variables according to the formulae. In addition, demographic variables and RF (U/l) and anti-CCP (U/l) were also recorded.

Risk of falling

To evaluate the risk of falling, five standardized performance tests were conducted as follows: (i) chair-rising test (CRT) [9], (ii) timed get up and go test (TUG) [10], (iii) Tinetti test (TIT) [11], (iv) tandem stand (TS) [9] and (v) tandem walking (TW) test [12]. They were performed according to the recommendations of the Austrian Geriatric Society.

The CRT is a timed test of muscle strength [13, 14]. The participant is asked to stand up and sit down from a chair (~45 cm height) five times in a row as fast as possible without using the arms. If a participant is not able to complete the test or needs >10 s, the risk for falls and immobility is increased [15].

In the TUG, an individual sits on a standard height armchair with his hands placed on the armrest. The person is asked to stand up (using the arms), walk 3 m at a normal speed, turn around, return to the chair and sit down again. The more time needed to complete the test, the greater the restriction of mobility and the higher the risk of falling. The TUG is recommended by several geriatric societies to identify patients who are likely to fall [16].

The TIT or performance-oriented mobility assessment is a reliable and valid tool to assess the fall risk of the elderly person [17–19] and was also probed in groups with specific neurologic diseases [20, 21]. It consists of a balance and a gait test. In total, 28 points can be achieved. The higher the score achieved, the better the performance. The TIT is considered to be the gold standard to evaluate mobility dysfunction in the elderly population [22].

TS and TW are balance tests. Like the CRT, the TS is part of the short physical performance battery [9]. For the TS, the time that a patient can hold a given position without losing balance is measured. The following three positions are checked: the side-by-side stand, the semi-tandem stand (the heel of one foot is placed on the side of the first toe of the other foot) and the full tandem stand (the heel of one foot is directly in front of the toes of the other). First, the participant is asked to stand in side-by-side position for 10 s. If balance can be kept, the person is requested to stand in semi-tandem position for 10 s and then in the full-tandem position for 10 s. The longer and the more positions one can hold, the better the performance. The TS was part of fall assessments in many studies [13, 23].

In the TW test the patient walks 2 m on a 5-cm-broad line heel to toe at normal speed. The false steps are counted. TW and TS showed good correlation with the risk of falling [24].

Statistical analysis

A descriptive statistical assessment was performed. The correlation between individual and composite measures of disease activity and the tests of the fall assessment were evaluated by Spearman's correlation analysis (r_s). We then performed linear regression analysis between the parameters CDAI, SDAI, DAS-28, HAQ-DI, TUG, CRT and TIT. We compared the fall assessment results across the disease activity categories (remission, low activity, moderate activity and high activity) using the Kruskal–Wallis test, which is a non-parametric test to compare whether more than two independent groups differ. All analyses were performed in IBM SPSS Statistics 19.

Results

Patient characteristics

Seventy-eight patients with RA participated in this study. Table 1 summarizes the patient characteristics.

Comorbidities

Thirty-five (44.9%) of the subjects suffered from hypertension, 2 (2.6%) had diabetes mellitus, 5 (6.4%) had polyneuropathy, 5 (6.4%) had atrial fibrillation and 35 (44.9%) had osteoporosis. Joint replacement had been performed in 19 (24.9%) of the cases, and 48 (61.5%) cases used vision aids. One patient had chronic hepatitis C and another one had pulmonary fibrosis. Three of the study participants used walking aids.

Falls and fear of falling

Of the 78 patients, 21 (26.9%) reported at least one fall during the preceding 12-month period. Four of them fell more times; 13 (61.9%) of those who fell sustained injuries, and 36 (46.2%) of the participants were fearful of falling. Table 2 shows the incidence of falls in different age groups. There were no differences between the groups aged >40 years. We found no statistically significant differences according to age between patients who reported a fall during the past 12 months and those who did not fall and participants who feared falling and those

who did not (P = n.s. by Mann–Whitney U-test). When comparing the results of TUG, CRT and TIT of patients with and without joint replacement by U-test, we found that those with joint replacement achieved numerically worse results in all three tests, but the differences were not statistically significant (data not shown).

Correlations between disease activity and fall assessment

The strongest correlation among all variables assessed with all fall tests was seen for the HAQ-DI, indicating—not surprisingly—that impairment of physical function was highly related to the risk of falls. In Table 3, these results as well as those of the correlations between other disease activity variables and the tests of the fall assessment are shown. The weakest correlations for individual variables were seen for SJC, EGA and CRP and higher correlations for patient-reported outcomes. Interestingly, we also found strong statistical associations for the composite measures: between the results of the CRT, TIT, TUG, TS and TW and CDAI (P = 0.01); between the DAS-28 and TIT, TUG, TS, TW (P = 0.01) as well as CRT (P = 0.05); and between SDAI and with CRT, TIT, TUG (P = 0.01) as well as TW (P = 0.05), but not with the TS.

The results of the regression analysis are shown in Fig. 1. Patients with higher CDAI, SDAI, DAS-28 and HAQ-DI values achieved poorer results on the TUG, CRT and TIT. Regression analyses underline the clinical relevance of the disease activity for the fall risk. For example, the regression coefficient for CRT and CDAI was 0.460. Therefore, a patient with a CDAI = 22.7 (high disease activity) needs on average 10 s more than a patient with a CDAI = 1.0 (in remission) needs to complete the CRT.

We also performed a Kruskal–Wallis test to compare the categories of the disease activity of CDAI, SDAI and DAS-28 with regard to the results of the TUG, CRT and TIT. We pooled patients with moderate and high disease activity. Table 4 summarizes the findings. For comparison, we used the median values. As expected, study participants in higher disease activity categories performed

Table 1 Characteristics of participants

Parameter	Value
Female, % (*n*)	84.6 (66)
RF positive, % (*n*)	61.6 (47)
Anti-CCP positive, % (*n*)	67.2 (50)
Age, years	59 (14.22) (19–83)
Disease duration, years	14 (11.45) (1–52)
HAQ-DI	0.82 (0.8) (0–2.75)
CDAI	7.6 (6.6) (0–28.5)
SDAI	8.98 (7.71) (0.19–40.1)
DAS-28	3.4 (1.15) (0.01–6.37)
SJC28	1 (2) (0–10)
TJC28	2 (3) (0–19)
CRP, mg/dl	1.38 (4.6) (0.02–40)
ESR, mm/h	28 (18) (0–82)
PGA, cm	3.32 (2.48) (0–9)
EGA, cm	0.86 (1.13) (0–5.8)
VAS pain	3.01 (2.49) (0–8.4)
Drug treatment	
DMARDs, %	51.3
Biologic, %	41
Steroids, %	42.1 (2.5–25)
(daily dose range in mg)	
NSAIDs, %	50
Analgesics, %	11.2

Values are the mean (S.D.) (range), unless otherwise specified.

Table 3 Correlations between fall assessment and disease activity parameters

		CRT	TUG	TIT	Tandem walk	Tandem stand
CDAI	r_s	0.460**	0.504**	−0.472**	0.310**	−0.277*
SDAI	r_s	0.400**	0.420**	−0.407**	0.287*	−0.223
DAS-28	r_s	0.314*	0.437**	−0.445**	0.328**	−0.325**
HAQ-DI	r_s	0.523**	0.620**	−0.676**	0.513**	−0.545**
Anti-CCP	r_s	0.148	0.162	0.023	0.087	−0.021
RF	r_s	0.123	−0.028	0.074	0.074	0.036
ESR	r_s	0.014	0.280*	−0.180	0.279*	−0.239*
CRP	r_s	0.241	−0.009	0.083	0.041	0.133
PGA	r_s	0.473**	0.577**	−0.520**	0.447**	−0.351**
EGA	r_s	0.261*	0.218	−0.259*	0.029	−0.001
VAS pain	r_s	0.441**	0.616**	−0.548**	0.513**	−0.404**
SJC	r_s	0.085	0.032	−0.050	−0.057	0.036
TJC	r_s	0.488**	0.394**	−0.385**	0.133	−0.203
Duration	r_s	0.288*	0.106	−0.68	0.223*	−0.204

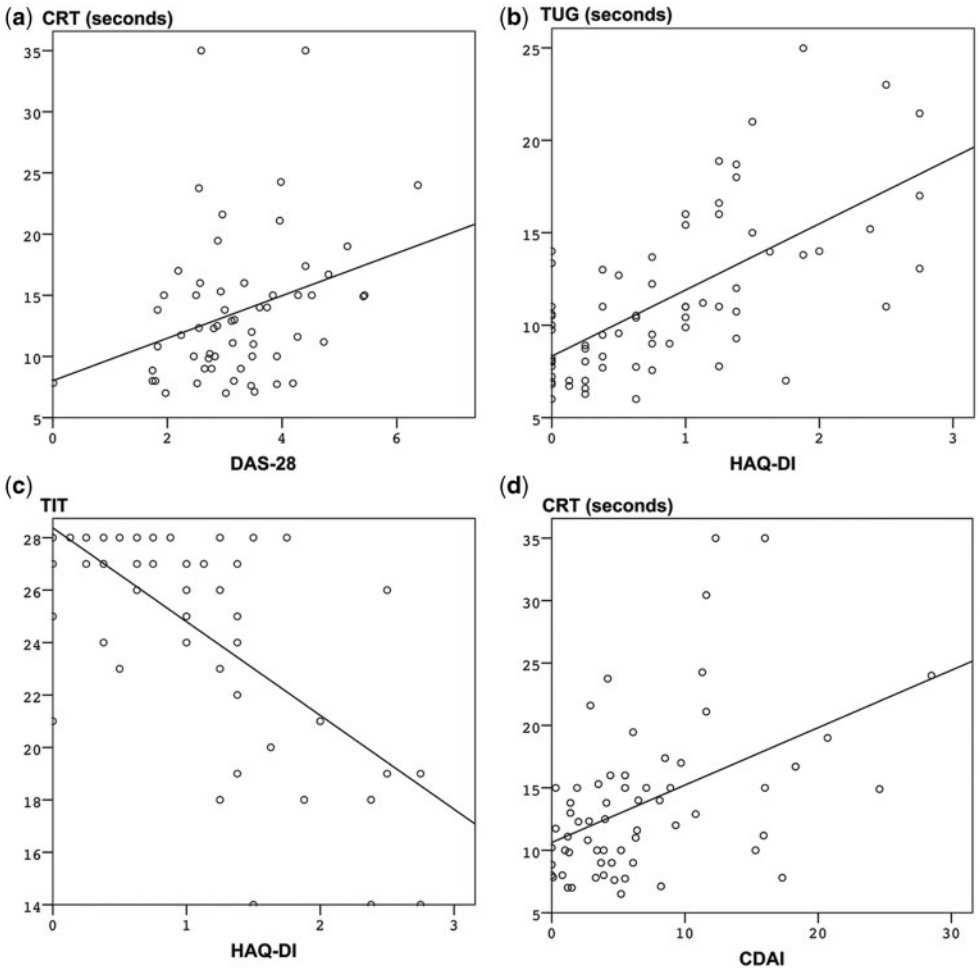
**$P \leqslant 0.01$, *$P \leqslant 0.05$.

Table 2 Fall prevalence, CDAI levels, CRT, TUG and TIT in different age groups

	<40 years	41–50 years	51–60 years	61–70 years	>70 years
Fallen, % (*n*)	0 (0)	30.8 (4)	25 (4)	30.4 (7)	35.3 (21)
CDAI	3.9 (3.3/15.3)	4.5 (1.4/6.1)	3.9 (1.4/6.3)	6.5 (4.2/12)	8.1 (4/12.3)
CRT	8.85 (8/10)	11.42 (9/13.8)	11.5 (10/16)	15 (8/19)	14 (12.3/16.7)
TUG	7 (6.92/7.77)	8.72 (8/10.5)	10.04 (7.5/12)	10.4 (7.8/12.7)	13.84 (11.1/17)
TIT	28 (28/28)	28 (27/28)	28 (26/28)	27 (25/28)	25 (21/27)

Given values are the median (25th/75th percentile), unless otherwise specified.

FIG. 1 Regression lines between disease activity parameters and fall assessment tests.



(**a**) DAS-28 and CRT ($r = 1.737$; $P < 0.014$), (**b**) HAQ and TUG ($r = 0.435$; $P < 0.001$), (**c**) HAQ-DI and TIT ($r = -0.528$; $P < 0.001$) and (**d**) CDAI and CRT ($r = 0.460$; $P < 0.001$).

worse than those in remission or low disease activity. At the TUG, significant differences were found between the categories for all three parameters: CDAI ($P = 0.001$) (Fig. 2a), SDAI ($P = 0.001$) and DAS-28 ($P = 0.012$). We found similar results for the TIT: CDAI, $P = 0.001$; SDAI, $P = 0.001$; DAS-28, $P = 0.002$. In the CRT, the findings were also significant for CDAI ($P = 0.002$) and SDAI, ($P = 0.015$), but not for the DAS-28 ($P =$ n.s.). We also analysed differences between age groups and the results of the fall assessment by Kruskal–Wallis test. With ageing, test performance was significantly worse in TUG ($P < 0.001$) and TIT ($P = 0.016$) and also in CRT, but did not reach statistical significance ($P = 0.054$). Because in our cohort the CDAI tended also to be higher in older patients (Table 2), we performed a general linear model to analyse the influence of disease activity when adjusted for age. CDAI levels significantly influenced all test results: CRT, $P < 0.001$; TUG, $P = 0.001$; and TIT, $P = 0.016$ (Fig. 2b).

Discussion

This study examined the relationship between disease activity and the risk of falling in patients with RA. Previous studies on this topic assessed primarily the prevalence of falls, with rates ranging from 33% to 54% for the preceding 12-month period [1–7]. In our cohort, 27% of the patients reported at least one fall during the preceding year. This number is a bit lower than, but nevertheless comparable to, most of the retrospective studies performed, which arrived at an incidence of 33–38% [1, 2, 4, 6], whereas prospective surveys found markedly higher fall rates; in a Dutch study 42%, and in a Japanese study 50%, of the patients fell during the 12-month study period [3, 7]. Differences in results between prospective and retrospective studies have been previously described [25]. Retrospective studies seem to underestimate the prevalence of falls because patients gradually tend to forget their falls [26]. This could also be the reason for a

TABLE 4 Comparison of the results achieved in different stages of disease activity

	CRT, median (*n*)	TUG, median (*n*)	TIT, median (*n*)
CDAI activity			
Remission	10.50 (18)	8.10 (20)	28 (20)
Low activity	12.25 (30)	9.47 (33)	28 (34)
Higher activity	17.85 (14)	13.68 (23)	25 (23)
SDAI activity			
Remission	10.50 (16)	8.10 (18)	28 (18)
Low activity	12.25 (30)	9.88 (33)	28 (34)
Higher activity	16.85 (14)	13.52 (22)	25 (22)
DAS-28 activity			
Remission	11.74 (17)	8.30 (19)	28 (19)
Low activity	11.70 (16)	9.10 (16)	28 (16)
Higher activity	14.45 (26)	12.35 (36)	26 (37)

lower fall frequency in our cohort and is a limitation of our study.

Among the patients interviewed in our study, 46% were fearful of falling. These results are comparable to the findings of Fessel and Nevitt (50%) [2] and are slightly lower than those of Jamison (60%) [4]. Interestingly, we could not find a statistically significant correlation between age and fear of falling.

According to previous studies, age and comorbidities are the strongest risk factors for falls in the elderly population [8, 27]. Thus, it is surprising that the incidence of falls in RA patients seems to be independent of age [1, 3–5, 7, 28, 29]. Armstrong *et al.* [1] showed that irrespective of age, one-third of RA patients aged >35 years report falls within the past 12 months. In our cohort, we also could not find a significant difference between the median age of patients who reported falls and those who did not, although, as seen in other geriatric populations, elderly RA patients performed worse in the functional test of mobility and balance, and within each age group, increasing disease activity negatively influenced functional ability (Fig. 2b). The relationship between age and falls in RA remains somewhat controversial and further research is needed.

In our examination, patients with total joint replacement performed worse on the TUG, CRT and TIT, but the results were not statistically significant. The number of patients with total joint replacement could have been too low to interpret the results. Previous studies have also demonstrated that various drugs can increase the risk of falling: glucocorticoids (dose-dependently) [3, 28], diuretics [1, 3], anti-hypertensives [3], antidepressants and sedatives [1]. In our cohort, patients who took anti-hypertensives performed worse in the fall assessment, whereas steroid intake did not influence the test results (data not shown). Also, people suffering from osteoporosis achieved worse results on the CRT, TIT and TUG (data also not shown).

Like most of the previous studies, we could not find a correlation between disease duration and increase in fall risk [1, 3–5]. This is remarkable insofar as an association between disease duration and severity of joint destruction and disability (HAQ-DI) has been demonstrated [30, 31]. Nevertheless, our results show the strongest correlation with the fall risk for HAQ-DI. Previous studies have also identified the HAQ-DI as a risk factor [2, 5, 7, 28]. The HAQ-DI is a composite of reversible activity-related and irreversible damage-related components [30], and it is likely that this composite nature provided the high correlation, even if the overall correlation is otherwise dominated by disease activity. Indeed, several core set variables, including pain (VAS pain and TJC), have a strong impact on the HAQ-DI [32].

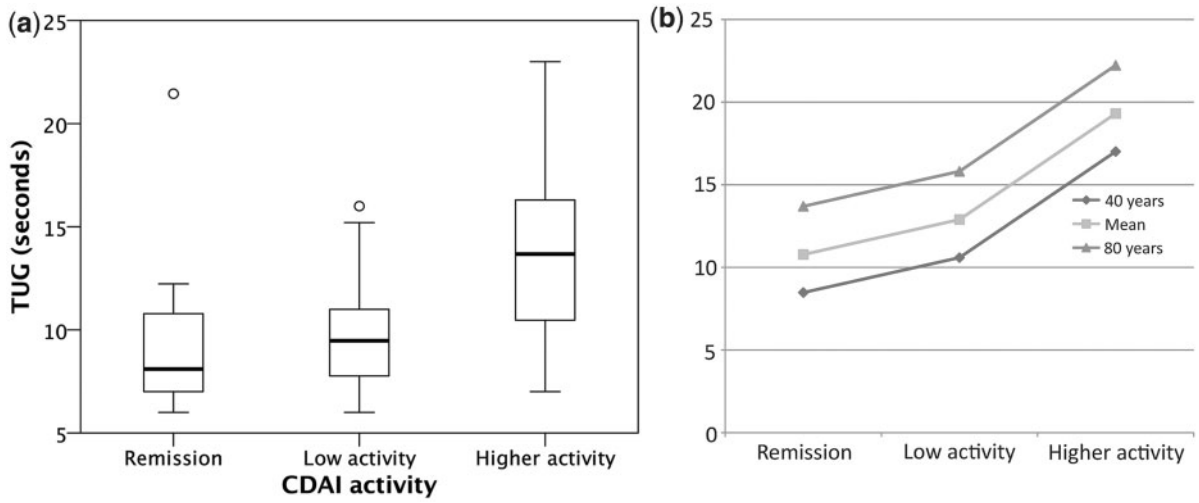
The results of previous studies regarding the correlation between disease activity and fall incidence are partly contradictory. An explanation for the inconsistent results could be the time point of examination. In previous studies, the variables of disease activity were either collected at the beginning of the study [3, 7] or at the end [1, 4, 28] and therefore usually not at the time when a fall occurred. In contrast, in the present study we evaluated the risk of falling measured by mobility tests and the disease activity on the same day. In particular, patient-reported outcomes had a strong effect. We did not find a correlation between either the presence of autoantibodies or increases in acute phase reactants CRP [3, 28] and ESR [3, 5] and fall risk. Further, similar to other studies, neither SJC [5, 28] nor EGA correlated. Thus the more objective measures of disease activity were much less related to the risk of falls than the patients' subjective assessments of pain, global disease activity, physical function and even TJCs. This is an important expansion of the value of patient-reported outcomes in RA. These results are in line with former studies, which demonstrated that chronic musculoskeletal pain increases the risk of falling [33, 34]. Pain is also the main factor for functional impairment in early RA [35].

Despite the preponderance of patient factors in the risk of falls, composite measure, CDAI, SDAI and DAS-28, which comprise patient-derived and non-patient-derived variables, all showed good correlations with the results of the fall assessment. This also confirms previous notions on the value of composite scores in assessing outcomes in RA [36]. Nevertheless, we found the strongest relationship of fall risks with CDAI, which does not comprise an acute phase reactant component, in contrast to SDAI and DAS-28. The Kruskal–Wallis test demonstrated that the risk of falling seems to increase with higher disease activity (Table 4), also when adjusted for age (Fig. 2b).

Our study has several limitations. The number of patients tested is low and we had no control group. Only a few patients with high disease activity participated in this study. Patients with high disease activity, and thus related pain and restricted mobility, seemed to agree less often to take part in a fall assessment. Patients with total joint replacement appear to have a higher fall risk [28] and so could have influenced the results of the current study.

Our results suggest that further research is needed. A study design where patients are examined several times in the course of treatment and with changes in

Fig. 2 Effects of disease activity on fall assessment outcome.



(**a**) Box plot of CDAI categories and results of the TUG. Patients in remission and with low activity achieved better results than those with higher activity on the TUG ($P = 0.001$). (**b**) Estimated marginal means of CRT in remission, low disease activity and higher disease activity adjusted for age at 57.6 years (mean), 40 years and 80 years.

disease activity could provide more detailed information on the relationship between disease activity and risk of falls, and possibly also on the mechanisms underlying this risk. Furthermore, the impact of radiographic changes on the risk of falling could be evaluated. Also, none of the examined variables distinguished between upper and lower extremities, especially because HAQ-DI and TJC28 focus more on the upper extremities.

In conclusion, we could identify several risk factors for falls in RA patients, which are related to disease activity. HAQ-DI, VAS pain, PGA, TJC, as well as the composite measures CDAI, SDAI and DAS-28 revealed the strongest correlations.

The parameters that showed the strongest correlation with the risk of falling can be obtained quickly and without extensive examination. This simplifies clinical application and allows rapid therapeutic interventions. In our view, risk of falling and its often severe consequences are still underestimated problems in RA patients. We suggest that in the case of pain or increased disease activity, patients should seek additional support from physiotherapists and occupational therapists for fall prevention.

Rheumatology key messages

- RA patients with higher disease activity have an increased risk of falling.
- In RA, patient-reported outcomes seem to be strongly related to fall risk.

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CONCISE REPORT

Serological changes in the course of traditional and biological disease modifying therapy of rheumatoid arthritis

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ABSTRACT

Objective To investigate changes of rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) during therapy with disease modifying antirheumatic drugs.

Methods We obtained clinical and serological data of patients from the treatment start and after 6 months of therapy. With non-parametric tests, we analysed changes of ACPA and RF levels between the two visits and the influence of treatment response. Furthermore, we analysed potential influential factors as disease chronicity, different therapeutics and the trend over 18 months.

Results 143 ACPA and RF positive patients were included. The median (25th/75th percentile) relative changes after 6 months were −35.6% (−63.3; −8.3) for RF and −15.2% (−40.0; 10.0) for ACPA ($p<0.001$ for both). Changes of RF levels were significantly greater than those seen for ACPA ($p<0.001$). The decrease of ACPA and RF was significantly higher in treatment responders ($p=0.034$ and $p=0.01$, respectively). Aside from changes in disease activity, only a short disease duration showed an independent effect on changes of RF levels ($p=0.087$).

Conclusions ACPA and RF levels decreased significantly after 6 months of therapy. Reductions of both autoantibodies were closely linked to a reduction of disease activity. RF declined faster, to a larger extent and in greater numbers of patients than ACPA.

Rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) are established markers in the diagnostic approach to rheumatoid arthritis (RA).[1] Besides their diagnostic relevance, RF and ACPA also have a prognostic value, since both are associated with more aggressive, destructive disease.[2–4] Moreover, high RF levels are related to extra-articular manifestations.[1] For these reasons, RF and ACPA are part of the 2010 RA classification criteria,[5] and considered bad prognostic markers in the European League Against Rheumatism (EULAR) recommendations for the management of RA.[6] Several studies examined changes of these autoantibodies (AAB) in the course of therapy, but especially for ACPA, findings were inconsistent.[7–9]

Given the current efforts to treat RA to a treatment target considering individual risk factors,[10] the presence and levels of these AAB are therapeutically highly relevant.[6] The aim of the present study was to evaluate the responsiveness of ACPA and RF levels during therapy of RA; in this context, we also aimed to consider the influence of individual therapeutic agents and treatment response with a special focus on the impact of disease duration and trend over time.

METHODS

Patients

We obtained data on RA outpatients who were seen at our clinic where data on every visit are prospectively documented in an observational database.[11] All participants fulfilled the 1987 American College of Rheumatology (ACR),[12] or more recently, the 2010 ACR/EULAR classification criteria for RA[5] and were recruited between February 2006 and October 2011. We selected patients with at least low disease activity, in whom a traditional or biological disease modifying antirheumatic drug (DMARD) was initiated, and identified those who were seropositive for ACPA and RF. For each patient, we selected only the treatment course with the longest follow-up period in order to maintain data independence in our analyses. All patients consented to an anonymous data analysis, and the local ethics committee had approved the data collection.

Study variables

At baseline and after 3, 6, 12 and 18 months of therapy, levels of RF (U/ml; positive >14 U/ml) and ACPA (U/ml; positive ≥5 U/ml) were obtained; ACPA levels >340 U/ml had not been further diluted, and since we were interested in changes in AAB levels, these patients were excluded. Furthermore, we collected patient and evaluator global assessments of disease activity; pain; swollen and tender joint count (SJC28 and TJC28); the Health Assessment Questionnaire Disability Index; C reactive protein (in mg/dl) and erythrocyte sedimentation rate (in mm/h). We mainly used the Simplified Disease Activity Index (SDAI) to measure disease activity.[13]

Statistical analysis

In most of our analyses, to account for the starting point (baseline level) of RF or ACPA, we evaluated relative rather than absolute changes within the first 6 months. All data were analysed by non-parametric statistics. To facilitate graphical illustration, we used a fractional rank depiction ('probability plots') with a 100% cap for worsening. All analyses were performed with SPSS.

We initially investigated whether overall significant serological changes are observable during 6 months of therapy, and if these changes were different for RF compared with ACPA. Next, we investigated the effects of treatment response, defined by SDAI50 criteria,[14] in relation to the observed changes in the serological measures. In addition to this categorical approach, we also used Spearman correlation to assess if individual disease activity components were associated with relative changes in AAB.

We then analysed the role of disease duration in AAB reactivity, comparing AAB changes in early (<12 months) and established RA (≥12 months), and of different therapeutics comparing methotrexate (MTX) with other traditional DMARDs, tumour necrosis factor α inhibitors (TNFi) and other biologicals. The analyses of treatment types and chronicity were then also adjusted for the differences in disease activity changes (a suspected major confounder) by calculating the % change of ACPA and RF per % change of SDAI.

Finally, we investigated the trend over time of ACPA and RF levels and of the SDAI. To this end, we selected patients who received the same therapeutic agent throughout a period of at least 18 months. Missing values were estimated by interpolation.

RESULTS

Study population

For our main analyses on changes after 6 months of therapy, data of 143 patients with complete datasets at at least these two time points were available. Clinical and demographic characteristics are shown in table 1.

Changes of ACPA and RF levels

The median (quartiles) absolute changes over 6 months of therapy were −9 U/ml (−42; 6) for ACPA (p<0.001) and −32 U/ml (−115; −4) for RF levels (p<0.001), as depicted in figure 1A. Median relative changes compared with baseline were −15.2% for ACPA (−40.0; 10.0) and −35.6% for RF (−63.3;−8.3), respectively. The changes of RF levels were significantly greater than those seen for ACPA (p<0.001).

Table 1 Baseline characteristics of participating patients. Except where indicated otherwise, values presented are median (25th percentile/75th percentile)

	Baseline	6 Months
Female (%)	83.2	
Age (years)	58 (47/67)	
Disease duration (years)	5.4 (0.36/13.9)	
Patients with early RA (%)	26.3	
SDAI	15.8 (9.8/22.4)	8 (4.6/14.1)
ACPA (U/ml)	107 (46/208)	85 (32/153)
RF (U/ml)	120 (38/274)	56 (23/175.5)
CDAI	13.8 (8.7/20.2)	7.6 (3.5/13.2)
DAS 28	4.3 (3.4/5)	3.4 (2.5/4.3)
HAQ	0.75 (0.125/1.375)	0.75 (0.13/1.25)
SJC 28	3 (2/6)	2 (1/3)
TJC 28	3 (1/6)	1 (0/4)
ESR (mm/h)	22 (14/54)	20 (11/40.5)
CRP (mg/dl)	0.8 (0.3/1.9)	0.35 (0.12/1)
EGA (mm)	21 (9/32)	10 (4/18)
PGA (mm)	46 (24/64)	23 (10/49)
VAS pain (mm)	43 (21/59)	22 (8/48)

ACPA, anti-citrullinated peptide antibodies; CDAI, clinical disease activity index; CRP, C reactive protein; DAS 28, disease activity score 28; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Effects of treatment response

The decrease of ABB was significantly higher in the 60 patients (42%) with treatment response than in those without (p=0.034 and p=0.01, respectively, figure 1B/C) (see online supplementary table S1 for ORs of improvement in serological markers among patients with different clinical response). The median absolute change for treatment responders was −17 U/ml (−68; 0) for ACPA and −43 U/ml (−143; −12) for RF, and the relative changes were −26.5% (−44.4; 0) and −47.9% (−66.7; −18.8), respectively. The serological changes in treatment responders were highly significant (ACPA: p=0.001; RF: p<0.001). In SDAI50, non-responders absolute and relative changes were −3.1 U/ml (−36; 9) and −7.5% (−27.0; 11.1) for ACPA and −18.0 U/ml (−96.0; 4.0) and −26.4% (−57.1; 3.3) for RF, respectively. In non-responders, the serological changes were clearly significant for RF (p<0.001), but failed to reach significance for ACPA (p=0.059). Correlations between changes of ACPA/RF and changes of individual disease activity variables are shown in table 2.

Effects of disease chronicity, different therapeutics and temporal trends

RF, but not ACPA levels, were more likely to improve within the first year from disease onset (p=0.039; p=0.316; figure 1D,E) than later. After adjusting for disease activity we still found a trend that RF titres decrease more clearly in patients with early RA, although differences were not statistically significant (RF p=0.087; ACPA p=0.802) (see online supplementary text and online supplementary table S2 for AAB changes on different types of treatment).

We could analyse AAB changes of 82 patients over 18 months. After 3 months, ACPA declined about 4.6% in relation to baseline, RF about 13.2% and SDAI about 23.5%; after 12 months, these values were 16.9%, 31.4% and 40.5%; and after 18 months, 23.8%, 35.2% and 44.3%, respectively.

DISCUSSION

In the current study, we show that ACPA as well as RF levels decrease significantly after 6 months of therapy. The findings presented are in line with previous studies, which mainly examined changes under individual TNFi.[9 15 16] RF seems to be more reactive than ACPA, as we found significantly higher decreases and a larger number of patients who improved with RF compared with ACPA. The smaller declines of ACPA levels may explain why discrepant views on changes of ACPA have been reported.[8 17]

Treatment responders had significantly higher ACPA and RF declines than non-responders. Previous studies found similar results.[9 15] Interestingly, in non-responders ACPA levels did not decline significantly, whereas RF levels still did. An explanation might be that DMARDs have a specific effect on RF production or that the decreases in RF levels indicate a subclinical therapeutic effect. While the finding could also indicate that ACPA might be a better marker to follow changes in disease activity, the much lower decrease of ACPA than RF in patients experiencing therapeutic efficacy and the correlation of clinical markers of disease activity with RF but not ACPA changes indicate that ACPA are overall less responsive to therapy, whether these effects are clinically visible or only subclinical.

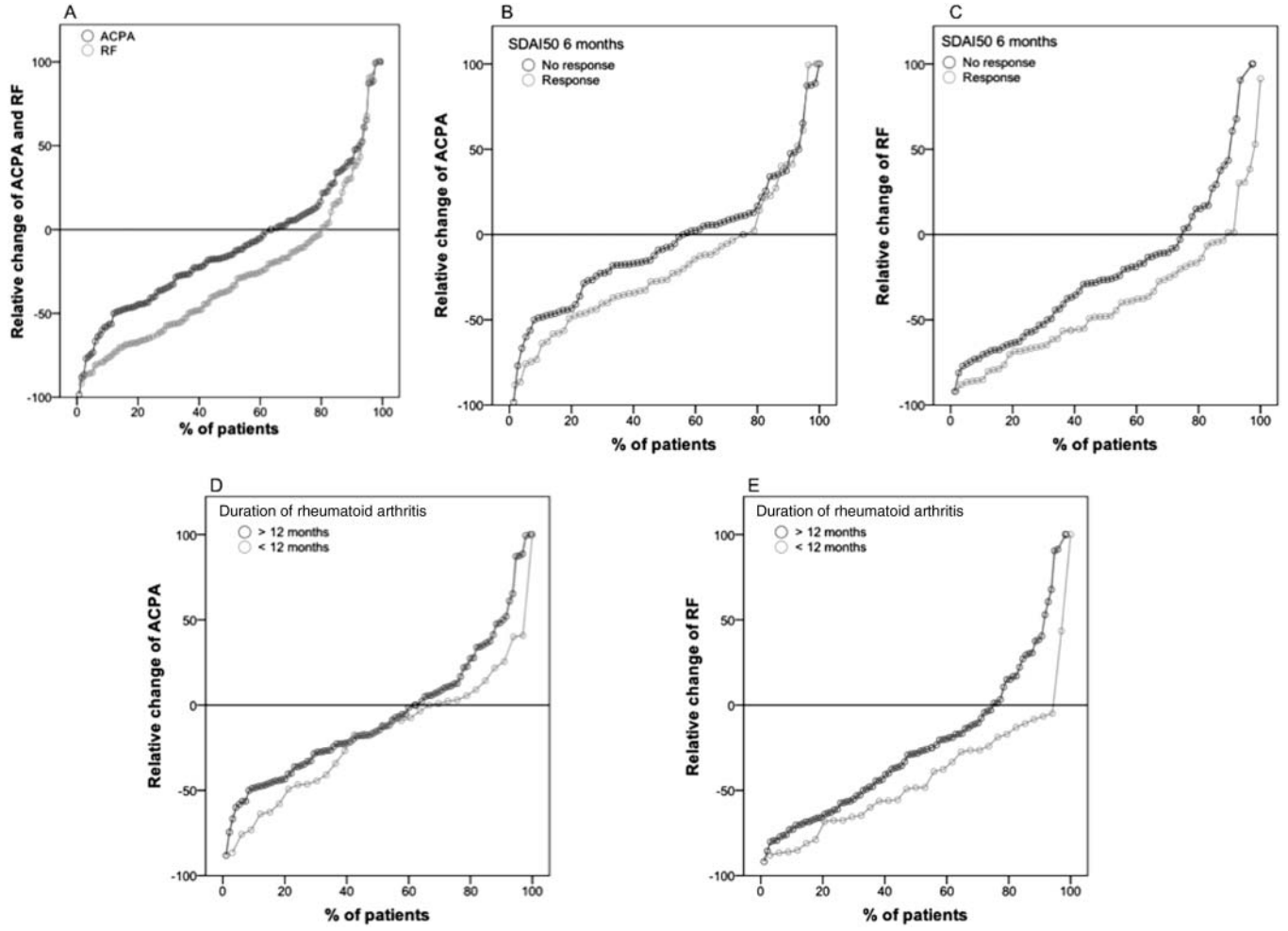

Figure 1 Probability plots of relative changes of anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF). Panel A shows the differences between relative changes of ACPA and RF. Panels B (ACPA) and C (RF) depict the influence of treatment response and panels D (ACPA) and E (RF) the differences between patients with early and established rheumatoid arthritis. SDAI, Simplified Disease Activity Index.

In simple correlation analyses, acute phase reactant changes were similarly associated with changes of ACPA and changes of RF, while changes of SJC, pain and patient global assessment were only correlated with changes of RF. The latter finding is very intriguing and one can only speculate that RF may be more strongly involved in activating cytokine production within the joints and that these local events are linked with swelling, but also with pain, which has been suggested associated with enhanced release of proinflammatory cytokines, like interleukin (IL)-6.[18] IL-6 is, vice versa, also involved in B cell differentiation and the development of antibody-producing plasma cells.[19] This might constitute a link between all these variables.

Table 2 Correlations (95% CI) between relative changes of ACPA/RF and relative change of SDAI, CRP, ESR, SJC, TJC, PGA, EGA, HAQ and pain

Change	ACPA (r)	RF (r)
SDAI	0.263** (0.085/0.425)	0.327** (0.154/0.480)
CRP	0.336** (0.164/0.488)	0.261** (0.082/0.423)
ESR	0.268** (0.090/0.429)	0.243** (0.063/0.407)
SJC	0.110 (−0.073/0.287)	0.236* (0.056/0.401)
TJC	0.174 (−0.009/0.345)	0.179 (−0.004/0.349)
PGA	0.143 (−0.040/0.317)	0.275** (0.098/0.435)
EGA	0.210* (0.029/0.378)	0.262** (0.084/ 0.424)
HAQ	0.063 (−0.121/0.243)	0.038 (−0.145/0.219)
Pain	0.054 (−0.129/0.234)	0.231** (0.050/0.396)
ACPA/RF	0.336 ** (0.164/0.488)	

Only patients with no missing data were used for analysis (n=116).
*p≤0.05 and **p≤0.01.
ACPA, anti-citrullinated peptide antibodies; CRP, C reactive protein; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC, swollen tender joint count; TJC, tender joint count.

RF level declines were greater in patients with a disease onset of less than 12 months; in accordance with the bad prognostic impact of RF, this could indicate that a prognostic difference can be made only at an early stage of the disease in many patients, consistent with the 'window of opportunity' theory in RA.[20] In contrast to a previous study,[21] changes of ACPA were not influenced by disease duration. This may be related to differences in study design and the small sample size of the published study.

One limitation in our study assessments was the fact that ACPA levels >340 U/ml were not further diluted; we were able to show that a comparable exclusion of the patients with the top RF levels did not affect the results (data not shown). In addition, we were not able to address the potential impact of changes in AAB levels on structural progression in our study: since both AAB are linked with radiological progression,[22] this is another limitation.

In conclusion, we were able to show that ACPA and RF levels decreased significantly after 6 months of therapy as well as subsequently and that decreases were closely linked to an improvement of disease activity. RF declined faster, to a larger extent and in greater numbers of patients than ACPA. Further research is needed to investigate whether reductions of ACPA and RF levels are associated with better structural and functional outcomes of RA in the longer term.

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Serological changes in the course of traditional and biological disease modifying therapy of rheumatoid arthritis

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