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The role of ultrasonography in monitoring long-standing rheumatoid arthritis: a pilot study

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Abstract

Objective: Rheumatoid arthritis (RA) is a condition that poses many diagnostic problems. As a result, it is often diagnosed too late, which makes effective treatment more difficult. The course of the disease is chronic, and it causes irreversible changes in the musculoskeletal system, as well as bone destruction, and this in turn impairs the proper monitoring of the treatment. Therefore, in order to assess the treatment's efficacy, as well as a clinical examination of the patient and laboratory tests, diagnostic imaging is being used more frequently in routine practice. The aim of this paper is to assess the usefulness of power Doppler ultrasonography in the assessment of MCP joints in patients with chronic RA (LSRA), in comparison with DAS28, X-ray, and MRI.

Material and methods: The study involved 26 patients with LSRA, treated with biologics. It lasted for a year. At the moment of enrolment, the condition had lasted for a minimum of 5 years, and DAS28 was > 5.1. The patients had visits every three months. During every visit, a PDUS test was performed and the DAS28 was determined. In the first and last month of the study the patients underwent X-ray and MRI tests.

Results: At the end of the study, the DAS28 of 26 (100%) patients was lower or equal to 3.2. Based on PDUS and MRI tests, no synovitis was found in 21 (81%) and 18 (69%) patients, respectively. According to the MRI results, radiological changes progressed in 5 (19%) of them. All patients who showed progress of radiological changes also had visible synovitis during their PDUS test.

Conclusions: PDUS in patients with LSRA can be helpful in selecting patients, who are likely to develop a progression of radiological changes.

Key words: ultrasonography, rheumatoid arthritis, MRI.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic connective tissue ddisease, the main symptom of which is chronic inflammation of symmetrical joints. In the early stages of the condition, the inflammation usually occurs in the hand and feet joints. Diagnosis of early RA (ERA) based on clinical symptoms is more difficult than diagnosing the advanced stage of the disease.

Synovitis, which is the essence of the condition, is very difficult to diagnose during a physical examination in the first weeks and months of RA. At this stage, traditional X-ray diagnostics do not show radiological changes typical for a developed stage of the disease. The diagnostic process of ERA, based on traditional methods, delays the start of proper treatment.

In the case of longstanding RA (LSRA), diagnostics is equally relevant, but its role may be completely different than in the case of ERA. This is due to the fact that LSRA causes irreversible changes, such as: synovial hypertrophy (SH) or destruction of joint surfaces. As a result, during a physical examination the source of joint pain in patients with LSRA may be misinterpreted – the pain

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is connected to destructive changes, as opposed to an inflammation, and to joint swelling, which is the result of SH. Due to the above-mentioned reasons, diagnostic imaging is required in order to objectively assess the condition's activity and monitor the treatment efficacy in patients with LSRA.

The newest classification criteria by the American College of Rheumatology/European League Against Rheumatism from 2010 are characterized by a high sensitivity in patients with RA for less than 2 years [1]. In the case of patients, who have been suffering from the symptoms of RA for less than 3 months, the sensitivity of the criteria is significantly lower [1]. This may results in missing the "window do opportunity", which is the right moment in the natural history of a disease, when a unique probability of the most efficient therapy occurs, leading do remission.

The term "treat to target" (T2T), which has been introduced into the new RA treatment guidelines, defines the aim of the therapy – to achieve remission as quickly as possible [2, 3]. According to EULAR recommendations, the treatment should be modified as soon as after 3 months, if it does not improve the condition, or after 6 months if remission is not achieved [4].

Assessing the activity level of synovitis, both at the moment of diagnosis and when monitoring the course of the disease, is an important diagnostic and prognostic tool for rheumatologists.

Currently, 2 methods of assessing synovitis are being used: magnetic resonance imaging (MRI) and ultrasonography (US).

MRI is the most precise tool to assess the synovium [5–7]. The high cost of the test and its duration adversely influence the possibility to widely apply this method in the diagnostic of RA and monitoring of RA treatment. In the case of ultrasounds, there are no such limitations. US is an accessible tool for rheumatologists. It is neither as time-consuming, nor as expensive as an MRI. It can be performed during a routine check-up, and its sensitivity in the imaging of synovitis and erosion is better than that of a psychical examination or X-ray [8].

Performing an ultrasound is especially valuable for "seronegative" patients, who are negative for the presence of the rheumatoid factor (RF), as well as anti-CCP antibodies [9]. In this group of patients an early diagnosis of RA is even more difficult, considering the new 2010 ACR/EULAR criteria [9].

Unfortunately, due to the limitations of the method, for instance the subjectivity of the test, as well as issues concerning the correct interpretation of its results, joint US was not included in the 2010 ACR/EULAR classification criteria. This does not mean, that the usefulness of US in the diagnostic and monitoring of RA is not appreciated. At the present, work aimed at defining coherent guidelines for joint assessment using US is in progress [10, 11]. This could allow to take this imaging method into account, when the guidelines are going to be updated.

Despite the lack of consistent criteria for assessing RA activity through US, it is a popular diagnostic tool in a rheumatologist's clinical practice.

Aim of the study

The purpose of this paper is to evaluate the usefulness of the power Doppler ultrasonography (PDUS) in monitoring the effectiveness of biological treatment in patients with LSRA, compared to other methods.

Due to the limited time, which can be allocated to each patient during a routine visit, the basis for this study was to reduce the amount of time spend on performing PDUS to a minimum. Therefore, only the MCP joints II to V in both hands were being assessed.

Material and methods

Twenty-six patients (19 women and 7 men) suffering from RA took part in the study (average age (standard deviation): 53.4 (12.1); duration of the condition: 15.8 (7.4) years, 85% anti-CCP positive, 92% RF positive). Patients enrolling in the study had to fit into the following criteria: DAS28 > 5.1, no treatment with biologics for at least 6 months prior to the study, except for infliximab and tocilizumab, and the duration of the condition had to be at least 5 years from the diagnosis.

All patients enrolled in the study were treated with infliximab in infusions of 3 mg/kg body weight (n = 8; 31%)) and with tocilizumab in infusions of 8 mg/kg body weight (n = 18; 69%), in accordance with the National Health Fund's treatment programme. The observational study lasted for a year. At enrolment each patient had an X-ray, MRI and PDUS of the MCP joints II to V in both hands, and DAS28 (CRP) was determined. During the PDUS the rheumatologist would choose the joint, which, in his opinion, was most severely inflamed. Each patient had PDUS assessment and joint assessment conducted by the same rheumatologist during whole study.

In the 3 and 6 month, patients had a PDUS of the MCP joint chosen at enrolment, and DAS28 was determined as well.

At the end of the study, in the 12 month of the treatment, patients had an X-ray and MRI (Philips Ingenia, 1.5 T, contrast agent: Gadovist) of both hands, a PDUS of the chosen joint, and DAS28 was determined.

PDUS was always performed using the same device, which was Esaote MyLab 70 gold with a linear transducer, at a frequency of 18 MHz. All PDUS tests were performed by two experienced rheumatologists, certified in

ultrasound examination. The PDUS results were evaluated on a scale from 0 to 3 (0 – no PD signal 1 – mild hyperaemia (PD signal covers up to 25% of the synovium), 2 – moderate hyperaemia (PD signal covers from > 25% up to 50% of the synovium), marked hyperaemia (PD signal covers more than 50% of the synovium) [12].

X-ray and MRI test results were interpreted by experienced radiologist, who work with the Rheumatology Clinic on a daily basis.

The study was conducted in accordance with the Declaration of Helsinki and was approved by an ethics committee at Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń. Every patient enrolled in the study received complete information regarding the study and consented to partake in the study, before enrolment.

Statistical analysis

The statistical analysis was performed in the MS Excel 2010 computer programme. The mean values between each visit were compared using the *t*-Student test. It was assumed, that for $p < 0.05$ differences were statistically significant.

Results

At enrolment, every patient had an X-ray, PDUS and MRI, which showed changes. During the MRI all patients were diagnosed with synovitis. During the PDUS every patient was diagnosed with, at least, grade II synovitis (Table I).

DAS28

The DAS28 value measured during every visit is presented in Table II. Up until month 6, a significant drop in the mean DAS28 was noted. Between the 6 and 12 month there was no significant difference between the average DAS28 values, although the condition's activity was assessed differently.

The number of painful and swollen joints was also reduced, as well as CRP and the assessment of the condition by the patient on a Visual Analogue Scale (VAS) (Table III). In the 3 month of the treatment, only one patient experienced no drop the condition's activity. In the 6 month of the study, 9 (35%) patients showed no improvement, compared to month 3.

X-ray and MRI

At the end of the study, using an MRI test, synovitis was diagnosed in 8 (31%) patients, which included 5 (19%) patients, who were diagnosed with progressive changes, and 3 (12%) patients who presented progression so severe, that it could be observed in an X-ray.

Seven (27%) patients presented with a contrast enhancement of the synovial membrane in an MRI, but it was deemed, that this is not necessarily a result of synovitis in the course of RA.

PDUS

In the PDUS, already at month 3, 18 (69%) patients were diagnosed with remission (PD signal less than 2).

Table I. Number of patients based on PD signal in the chosen joint during each visit

Visit	PD 0	PD I	PD II	PD III
Month 1	0	0	16	10
Month 3	7	11	8	0
Month 6	11	10	5	0
Month 12	13	8	5	0

Table II. Number of patients based on disease activity level according to DAS28 and the DAS28 mean value during each visit

Visit	Remission (2.6 ≥ DAS28)	Low disease activity (3.2 ≥ DAS28 > 2.6)	Moderate disease activity (5.1 ≥ DAS28 > 3.2)	High disease activity (DAS28 > 5.1)	Mean DAS28 ± standard deviation
Month 1	0	0	0	26	5.6 ±1.1
Month 3	3	1	21	1	3.9 ±0.8*
Month 6	7	10	9	0	2.9 ±0.9*
Month 12	9	17	0	0	2.5 ±0.7*

**significant changes compared to Month 1, p < 0.05*

Table III. Number of painful and swollen joints during subsequent visits, based on DAS28

	Month 1	Month 3	Month 6	Month 12
TJC	309*	125*	88*	48*
SJC	159*	46*	39*	26*
CRP (mean ± SD)	36.6 ±34.4	16.6 ±17.4	3.3 ±5.1*	1.6 ±2.6*
VAS (mean ± SD)	69.1 ±15.1*	42.6 ±17.4*	34.5 ±16.8*	32.9 ±14.2*

TJC – tender joint count; SJC – swollen joint count; significant changes compared to month 1, $p < 0.05$*

During future visits, in patients, who were in remission or presented with low disease activity (LDA), no recurrent synovitis was found. In later months, the change dynamics were a lot slower. At the end of the study the number of patients with remission or LDA increased by 4. Overall 21 (81%) patients were in remission.

Five patients, who experienced persistent synovitis in the 3 month of study (at least grade II during PDUS), presented with progression of radiological changes in the MRI test.

Discussion

With the introduction of the "window of opportunity" term and the T2T strategy, more and more rheumatologists understand the need to implement new diagnostic tools, as well as for diagnosing RA and monitoring the effectiveness of the treatment. There is an agreement, that both MRI and US are valuable diagnostic tools. MRI is considered to be the more sensitive method. Due to its accessibility, low cost and short time of examination, US is the basic tool in diagnostic imaging.

Although no one seeks to discredit the importance of the ultrasound in therapeutic proceedings, there are still no coherent guidelines for the assessment of RA clinical activity based on US/PDUS.

The main problem with introducing US to the RA diagnostic criteria is the choice of joint and the number of joints to be assessed. A routine ultrasound is not time-consuming, but if too many joints were to be assessed, this would significantly prolong the visit, which would cause reluctance in both physicians and patients.

At the same time, it is being vastly reported, that the standard methods of assessing disease activity, such as: DAS, DAS28, DAS44, and relatively new indicators like Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index are limited as well [13, 14]. The main problem with these indicators is the insufficiently precise physical assessment of joint pain and swelling. In patients with LSRA joint pain is often associated with irreversible destructive changes, which occur in the course of the disease, not with inflammation [15]. Furthermore, a lack of joint swelling does not mean there is no inflammation in the synovial membrane.

On the other hand, synovial hypertrophy doesn't have to indicate inflammation. During a physical examination, synovial hypertrophy resulting from an inactive inflammation, results in the joint being diagnosed as swollen.

Many studies have proven, that even in patient in remission, synovitis can be observed during an MRI or US [16]. Even though those are subclinical observations, they can lead to irreversible changes in the long run. They are a means to obtaining information, which can't be obtained from disease indicators, such as: DAS, CDAI or SDAI.

It is believed now, that several to a dozen or so joints should be assessed using US. Most authors agree, that MCP joints are the ones, which are most likely to be inflamed in the course of RA [17]. Using the sonographic activity score (SAS 1) indicator only 1 MCP joint, chosen during the first visit, is examined, and the choice is based on the strongest PD signal in the synovial membrane, which indicates an inflammation [17].

In this study, in order to imitate the real working conditions of doctors in the Rheumatology Clinic and due to the limited time of a routine visit, we used the SAS 1 indicator to assess LSRA activity.

At month 3, significant improvement was diagnoses during the PDUS test. During subsequent visits, no significant changes in PDUS assessment were found. An inflammation in the observed joint persisted. These results do not correlate with the changes in DAS28, which gradually improved during every visit. According to DAS28 the number of patients in remission was increasing. When the study ended, all patients achieved LDA or remission (DAS28 ≤ 3.2). However, during PDUS and MRI tests, respectively 5 (19%) and 8 (31%) patients were diagnosed with synovitis, which indicates persisting disease activity at the subclinical level.

The most significant observations in this study concerned 5 patients, who were diagnosed with progression of radiological changes after one year of treatment. Those were patients, who were diagnosed with LDA based on DAS28. However, during the whole study, synovitis was visible during the PDUS test. According to the data presented in Table I, those five patients comprised respectively 63%, 100% and 100% in months 3,

6 and 12 of the study, who consistently presented with a PD signal of at least grade II. This could indicate, that a persistently strong PD signal in the first three months of treatment, is a sign of a bad prognosis. Naturally, this should be confirmed on a larger group of patients.

On the other hand, amongst patients, who were diagnosed with remission (PDUS signal less than II), at the end of the study 3 (12%) were diagnosed with synovitis during an MRI. This means, that monitoring only one joint is not sufficient to diagnose subclinical changes in LSRA in the longer perspective. Even in patients experiencing a less aggressive course of the disease, subsequent irreversible changes can develop over the course of several years.

Based on the results presented above, we can conclude, that in the first months of treatment patients with LSRA can be examined based on a small number of joints. The main factor of a bad prognosis at that time is persisting synovitis. In order to control the condition for a longer period of time on the subclinical level, a gradual increase in the number of US tested joints may be necessary.

PDUS may be a strong predictive tool in the assessment of treatment effectiveness, and it can be helpful when modifying the treatment, especially with regard to the T2T strategy.

Naturally, the question remains how therapy modifications could influence stopping the progression of radiological changes. The question to this answer is not obvious, as the results of the TaSER study indicate [18]. The study concerned patient with ERA. 111 patient were enrolled and divided into two groups: a Control Group consisting of 57 patients, and an Intervention Group consisting of 54 patients. Both groups were treated with the established disease-modifying antirheumatic drugs therapy. In the control group, treatment modifications were implemented based on DAS28 values, and in the intervention group based on both DAS28 and US results. Based on the results in the intervention group, usually a more aggressive treatment was implemented, compared to the control group. However, intensifying the treatment did neither significantly improve the results of the imaging test, nor the clinical assessment [18]. The authors suggested, that in spite of the lack of differences between the groups, monitoring patients using US, may help to achieve better long-term effects by reducing subclinical symptoms. They also pointed out, that the most significant changes were visible in the first three month of therapy [18].

In previous studies it was also suggested, that the progress in US diagnostic, especially due to increasing the transducer frequency, used to examine the joints, could increase the diagnostic value of US. In our study we used a 18 MHz transducers, and the studies, to which we compared our results, used mainly 10–16 MHz transducers. After comparing the results of both studies, we can conclude, that increasing the frequency of the emitted ultrasounds has significant influence on the correlation between US results and the DAS28 assessment. MRI tests are more sensitive in diagnosing inflammations than US. Since the beginning of our study, a new blood flow imaging technology, called super microvascular imaging (SMI), has become available, and it could increase synovial membrane blood flow assessment sensitivity [19]. This could reduce the disparities in sensitivity between US and MRI tests. Due to the high imaging sensitivity, less experienced ultrasonographers could interpret it as inflated flow in a semiquantitative assessment.

Taking into account the topic of our paper, Peluso et al. [20] conducted very interesting research as well. 48 patients with ERA and 46 with LSRA with at least 6 months of remission (DAS < 1.6) took part in the mentioned study. Despite stable remission based on DAS, only 44% of the patients with ERA and 17% of patients with LSRA were diagnosed with remission in an US test (no PD signal and no SH). Inactive synovitis (no PD signal, visible SH) was diagnosed in 15% and 52% of the patients. This indicated, that as the condition progresses, the synovial membrane thickens irreversibly. The results also suggest, that an US test in patients with ERA has more of a prognostic value for sustaining remission, than in patients with LSRA [20].

These results are consistent with the results of our study. PDUS was more helpful in selecting patients, who are likely to develop a progression of radiological changes. It should also be noted, that in our study PDUS diagnostic was significant in the 3 month of treatment. Only some patients, who were diagnosed with grade II synovitis using PDUS, at this stage of the study, developed a progression of radiological changes after a year of treatment.

Changes occurring in the course of RA clearly suggest, that there should be a distinction between patients with ERA and LSRA. Although in both cases PDUS is very important, the information we gather based on it are different. In patients with ERA it seems, that the examination is aimed primarily at diagnosing active synovitis, and in patients with LSRA it allows to diagnose inactive SH in order to eliminate the possibility of wrongly diagnosing swelling.

Conclusions

In patients with LSRA, PDUS should be performed regularly in the first weeks since the change of treat-

ment. A rapid drop in the PD signal was characteristic for patients, who were in remission after one year, based on DAS28 and PDUS, and, what's most important, no radiological progression was found.

The strong PD signal persisting in the first three months, may suggest a further progression of the disease and a progression of radiological changes.

Reducing the number of joints assessed in the US test in patients with LSRA, does not adversely affect the routine work of a rheumatologist, and even in the case of a "busy clinic", this should be included in standard procedures. This allows to gain detailed information, which are crucial in applying modern therapies and the T2T strategy.

The authors declare no conflict of interest.

References

1. Migliore A, Bizzi E, Petrella L, et al. The challenge of treating early-stage rheumatoid arthritis: the contribution of mixed treatment comparison to choosing appropriate biologic agents. BioDrugs 2016; 30: 105-115.
2. van Nies JA, Tsonaka R, Gaujoux-Viala C, et al. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden early arthritis clinic and ESPOIR cohorts. Ann Rheum Dis 2015; 74: 806-812.
3. Lukas C, Combe B, Ravaud P, et al. Favorable effect of very early disease-modifying antirheumatic drug treatment on radiographic progression in early inflammatory arthritis: data from the Étude et Suivi des Polyarthrites IndifféRenciées récentes (study and followup of early undifferentiated polyarthritis). Arthritis Rheum 2011; 63: 1804-1811.
4. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76: 960-977.
5. Szkudlarek M, Klarlund M, Narvestad E, et al. Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. Arthritis Res Ther 2006; 8: R52.
6. Sudoł-Szopińska I, Mróz J, Ostrowska M, et al. Magnetic resonance imaging in inflammatory rheumatoid diseases. Reumatologia 2016; 54: 170-176.
7. Mathew AJ, Danda D, Conaghan PG. MRI and ultrasound in rheumatoid arthritis. Curr Opin Rheumatol 2016; 28: 323-329.
8. Wakefield RJ, Gibbon WW, Conaghan PG, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum 2000; 43: 2762-2770.
9. Ji L, Deng X, Geng Y, et al. The additional benefit of ultrasonography to 2010 ACR/EULAR classification criteria when diagnosing rheumatoid arthritis in the absence of anti-cyclic citrullinated peptide antibodies. Clin Rheumatol 2017; 36: 261-267.
10. Horton SC, Tan AL, Wakefield RJ, et al. Ultrasound-detectable grey scale synovitis predicts future fulfilment of the 2010 ACR/EULAR RA classification criteria in patients with new-onset undifferentiated arthritis. RMD Open 2017; 3: e000394.
11. Naredo E, Wakefield RJ, Iagnocco A, et al. The OMERACT ultrasound task force--status and perspectives. J Rheumatol 2011; 38: 2063-2067.
12. Fiocco U, Ferro F, Vezzù M, et al. Rheumatoid and psoriatic knee synovitis: clinical, grey scale, and power Doppler ultrasound assessment of the response to etanercept. Ann Rheum Dis 2005; 64: 899-905.
13. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005; 23: 100-108.
14. Dejaco C1, Duftner C, Wipfler-Freissmuth E, et al. Ultrasound-defined remission and active disease in rheumatoid arthritis: association with clinical and serologic parameters. Semin Arthritis Rheum 2012; 41: 761-767.
15. Kirwan JR. Links between radiological change, disability, and pathology in rheumatoid arthritis. J Rheumatol. 2001; 28: 881-886.
16. Ogishima H, Tsuboi H, Umeda N, et al. Analysis of subclinical synovitis detected by ultrasonography and low-field magnetic resonance imaging in patients with rheumatoid arthritis. Mod Rheumatol 2014; 24: 60-68.
17. Grassi W, Gaywood I, Pande I, et al. From DAS 28 to SAS 1. Clin Exp Rheumatol 2012; 30: 649-651.
18. Dale J, Stirling A, Zhang R, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. Ann Rheum Dis 2016; 75: 1043-1050.
19. Li W, Liu F, Zhu J, et al. Superb Micro-Vascular Imaging improving inflammatory flow blood sensitivity in patients with rheumatoid arthritis. Int J Clin Exp Med 2016; 9: 19930-19934.
20. Peluso G, Michelutti A, Bosello S, et al. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis 2011; 70: 172-175.