Do new and old biomarkers of early undifferentiated arthritis correlate with the Arthritis Impact Measurement Scales?

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Abstract

Objective

In early undifferentiated arthritis (EUA), the relationship between inflammatory biomarkers and disability is still unclear. The aim of this study was to correlate inflammatory biomarkers with the Arthritis Impact Measurement Scales (AIMS) in EUA.

Methods

Seventy patients with EUA were compared with 20 patients with established rheumatoid arthritis (RA). The association of AIMS [mobility, physical impairment (PI), dexterity, household activities, activities of daily living (ADL), social activity, pain, anxiety, depression] with serum laboratory [phase acute reactants, calprotectin, interleukin-6, tumour necrosis factor (TNF)-α, rheumatoid factor, anti-nuclear and anti-citrullinated peptide antibodies, HLA-DRB], clinical [Clinical Disease Activity Index (CDAI), fatigue, pain and stiffness NRS], x-ray and ultrasound biomarkers was analysed with non-parametric Spearman's rank correlation and Mann-Whitney U tests.

Results

*No differences in AIMS were found between EUA and established RA patients, or between EUA patients that evolved into early RA (n=17) and those that remained EUA (n=53) at six months of follow-up. In EUA, erythrocyte sedimentation rate correlated with mobility impairment, PI and depression (p=0.04, p=0.03 and p=0.022, respectively), TNF-α correlated with PI (p=0.01) and calprotectin with anxiety (p=0.02). HLA-DRB1*11-positive EUA patients had lower ADL deficiency (p=0.006), depression (p=0.0004) and anxiety (p=0.01). CDAI correlated with PI (p=0.01) and pain (p=0.01), fatigue with PI (p=0.0001) and ADL (p=0.009), stiffness with PI (p=0.01), and Power Doppler ultrasound synovitis with PI (p=0.02) and pain (p=0.007).*

Conclusion

*In EUA, physical and mood disorders are associated with new and old inflammatory serological, clinical and imaging biomarkers. HLA-DRB1*11-positivity may be protective against these disease-related features.*

Key words

early undifferentiated arthritis, rheumatoid arthritis, biomarkers, arthritis impact measurement scales, HLA-DRB

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Introduction

Although one of the primary aims of treatment is to reduce the consequences of rheumatoid arthritis (RA) on the quality of life, unfortunately traditional disease activity measures often fail to estimate the real disease impact on patient impairment, disability and handicap, as defined by the World Health Association of patients' life damage. Impairment is defined as the loss of anatomical and psychological function, and disability as the inability to perform normal activities; handicap refers to the disadvantage of life resulting from impairment and disability.

The Arthritis Impact Measurement Scales (AIMS) is a reliable and validated self-administered health scale questionnaire that tries to summarise the aforementioned aspects in patients with RA (1, 2). In early disease phases, the impairment and disability parameters taken into account might be conditioned by the patient's personal beliefs that could hamper a univocal interpretation of disease-related symptoms. Interestingly, serological, clinical and imaging biomarkers may be useful to predict the evolution of undifferentiated arthritis (UA) into established RA (3). However, the possible correlation of such predictive biomarkers and quality of life parameters of UA patients has not been investigated.

The objective of our work was to compare the AIMS parameters of patients with early UA (EUA) with those of established RA patients and to investigate the correlation between AIMS and both new and old inflammatory biomarkers in EUA.

Materials and methods

Data from patients with EUA (referred to our hospital from April 2016 until March 2017) were retrospectively collected at the San Giovanni di Dio Hospital Early Arthritis Clinic (Florence, Italy). A total of 70 consecutive patients older than 18 years with a recent-onset EUA (up to 12 months before the visit), fulfilling the Visser Criteria (4) and not previously treated with steroids and DMARDs were selected, after exclusion of subjects with infections, tumours, neurological disorders (multiple sclerosis and cognitive impairment), fibromyalgia and crystal-related arthritis. All EUA patients were followed-up for six months to investigate the possible disease evolution into early RA (ERA, diagnosed with EULAR/ACR 2010 criteria). Informed consent for anonymous analysis and publication of data was signed by each patient enrolled following the guidelines for investigation on human beings of the institutional review board.

AIMS questionnaire, laboratory biomarkers, physical examination and imaging were performed at the same time at first visit. All patients filled the Italian version of AIMS (2) including 9 scales each consisting in 4–7 questions normalised to 0-10 (0 representing good and 10 poor status, respectively): mobility, physical activity, dexterity, household activities, social activity, activities of daily living (ADL), pain, anxiety and depression. AIMS results of EUA patients were compared with questionnaire data from 20 age- and sex-matched patients with established RA (almost 3 years of disease). Moreover, AIMS results of the 17 EUA patients that evolved into ERA were compared to those of the 53 patients that remained EUA at six months of follow-up.

Serum samples were collected and tested at the San Giovanni di Dio Immunology and Allergology Laboratory, Clinical Pathology Laboratory and Genetic Laboratory Usl Tuscany Center (Florence, Italy) for erythrocyte sedimentation rate (ESR) (mm/hour), C reactive protein (CRP) (mg/dL), antinuclear antibodies (ANA) by IIF using HEp-2 cells (Euroimmun, Lübeck, Germany), extractable nuclear antigen (ENA) antibodies, anti-double-stranded (ds)DNA antibodies by multiplex immunoassay and Crithidia luciliae immunofluorescence test, anti-citrullinated peptide antibodies (ACPA) (Anti-CCP EDIA™; Euro-Diagnostica, Malmö, Sweden), rheumatoid factor (RF) IgM (N Latex RF; Siemens AG, Munich, Germany), tumor necrosis factor (TNF)-α (Human TNF-alpha Quantikine Immunoassay; R&D Systems, Inc., Minneapolis, MN, USA), calprotectin (Calprest, Eurospital, Trieste, Italy), interleukin (IL)-6 (Human

Table I. Demographic and clinical features and Arthritis Impact Measurement scales (AIMS) parameters of patients with early undifferentiated arthritis (EUA), patients with established rheumatoid arthritis (RA), and EUA patients stratified according to the evolution into early RA (ERA) at six months of follow-up.

	Mobility impairment	Physical activity impairment	Dexterity impairment	Household activity impairment	Social activity impairment	Activities of daily living	Pain	Depression	Anxiety
EUA (n=70)*	3.92 ± 0.15 (3.61-4.23)	2.75 ± 0.31 (2.12-3.37)	8.37 ± 0.31 (7.74-9.01)	9.32 ± 0.22 (8.88-9.77)	6.78 ± 0.3 (6.17-7.39)	3.83 ± 0.24 (3.35-4.31)	9.76 ± 0.36 (9.04-10.49)	2.85 ± 0.37 (2.11-3.59)	5.14 ± 0.39 (4.35-5.94)
RA (n=20)**	3.0 ± 0.62 (1.58-4.41)	4.15 ± 1.08 (1.69-6.61)	8.84 ± 0.69 (7.26-10.42)	10.03 ± 0.34 (9.24-10.82)	5.67 ± 0.6 (4.31-7.03)	3.376 ± 0.52 (2.17-4.57)	7.87 ± 1.07 (5.45-10.30)	2.9 ± 0.75 (1.19-4.61)	4.94 ± 1.15 (2.28-7.59)
EUA evolved into ERA (n=17)***	4.04 ± 0.29 (3.42-4.66)	2.72 ± 0.65 (1.32-4.10)	8.04 ± 0.88 (6.15- 9.93)	9.28 ± 0.53 (8.14-10.42)	7.29 ± 0.61 (5.99-8.60)	3.82 ± 0.62 (2.50-5.13)	10.44 ± 0.58 (9.19-11.68)	3.48 ± 0.93 (1.48-5.47)	4.87 ± 0.81 (3.14-6.61)
EUA not evolved into ERA (n=53)****	3.89 ± 0.18 (3.53-4.25)	2.76 ± 0.36 (2.06-3.46)	8.48 ± 0.32 (7.85-9.11)	9.34 ± 0.22 (8.86-9.82)	6.62 ± 0.35 (5.93-7.31)	3.84 ± 0.25 (3.35-4.33)	9.55 ± 0.44 (8.69-10.41)	2.67 ± 0.39 (1.89-3.44)	5.23 ± 0.46 (4.33-6.13)

*27 male and 43 female, mean ± SD age 57.9±16.8 years, mean±SD CDAI 17.79±7, 4/70 ACPA-positive, 7/70 RF-positive, and 9/70 x-ray erosive.
**6 male and 14 female, mean ± SD age 58.4±21.1 years, mean±SD CDAI 18.9±5.1, 6/20 ACPA-positive, 14/20 RF-positive, and 100% x-ray erosive.
***7 male and 10 female, mean ± SD age 60±13.43 years, mean±SD CDAI 18.85±4.14 at baseline and 13.11±8.36 at follow-up, 4/17 (high titre in 3/17) ACPA-positive at baseline and 4/17 at follow-up, 7/17 (high titre in 5/17) RF-positive at baseline and 10/17 at follow-up, 2/17 x-ray erosive at baseline and 6/17 at follow-up.
****20 male and 33 female, mean ± SD age 56.6±15.8 years, mean±SD CDAI 17.47±8.43 at baseline and 11.6±8.8 at follow-up, 0/53 ACPA-positive and 0/53 RF-positive at baseline and follow-up, 7/70 x-ray erosive at baseline and 9/70 at follow-up.
AIMS values are expressed as mean ± SEM and lower and upper 95% confidence interval.
ACPA: anticitrullinated autoantibodies; CDAI: Clinical Disease Activity Index; RF: rheumatoid factor.

IL6 Instant Enzyme-linked Immunosorbent Assay), and HLA-DRB aplotype analysed with inverse hybridisation PCR (One Lambda, Canoga Park, CA, USA).

At clinical examination, patients were evaluated with 0–76 Clinical Disease Activity Index (CDAI) (5) (a composite index resulting from the sum of 28 tender and swollen joints, 0–10 physician and 0–10 patient activity of disease evaluation), and assessed for fatigue, pain at clinical examination and stiffness 0–10 numerical rating scale (NRS), and duration of morning stiffness in minutes. Affected joints were investigated by longitudinal and transverse ultrasound (US) examination performed by an experienced sonographer (FB) with a MyLab70 XVG machine (Esaote SpA, Genoa, Italy, multifrequency linear probe 12–15 MHz). All images were saved in a digital archiving computer system. The US intra-observer agreement, tested on the same machine, has been previously published (6) reporting good results (unweighted κ test=0.90). Synovitis (defined as echogenic non-compressible intra-articular synovial vascularisation with Power Doppler [PD] signal), tendon tenosynovitis or peritendinitis (*i.e.* hypoechoic thickened tissue with or without fluid within the flexor tendon sheath or around extensor tendons, respectively, seen in 2 perpendicular planes, displaying PD signal), and bone erosions (*i.e.* interruptions of the bone profile on two perpendicular scanning planes) were investigated (7). Maximal scores of PD (PRF of 750 Hz, gain 53–55% dB) and erosions were semi-quantitatively evaluated as 0-3 (for PD, 0 = absence, 1 = mild, single vessel, 2 = moderate, confluent vessels, and 3 = marked vessels in over half of area; for erosions, 0 = normal, 1 = cortical break <2 mm, 2 = cortical break 2–4 mm, and 3 = cortical break >4 mm) (8). Baseline hand and foot x-ray scans were scored with Simple Erosion Narrowing Score (SENS) (9), a simplified bimodal scoring method (0 = absent, 1 = present) of erosions and narrowed joints, with a maximum total score of 86.

Descriptive statistics were expressed as mean ± standard deviation (SD) or standard error of the mean (SEM), 95% lower and upper confidence intervals of mean (CI), and percentage for categorical variables, as appropriate. Normal distribution of parameters was verified by Kolmogorov-Smirnoff and D'Agostino tests. A *p*-value less than 0.05 was considered statistically significant. Differences in AIMS data and binary laboratory parameters (positive *vs*. negative) were evaluated with the non-parametric Mann-Whitney U test. The correlation of AIMS (stratified for different classes of age) with laboratory, clinical and imaging parameters was analysed with non-parametric Spearman's rank correlation test.

Results

AIMS results were not significantly different between 70 patients with EUA and 20 age- and sex- matched patients with established RA (disease duration 4.2±1.1 years) (Table I).

At baseline, EUA patients presented high titre (>3 times respect to normal values) of ACPA and RF in 3/70 and 5/70, respectively, with monoarticular onset in 9/70, oligoarticular in 46/70 and poliarticular in 15/70 (tender joint count: mean±SEM 2.47±0.22, 95% CI 2.02–2.91; swollen joint count: mean±SEM 3.2±0.53, 95% CI 2.21–4.36). In all cases, at baseline, x-ray SENS resulted from the sum of erosions extending less than 25% of joint, and no narrowed joints were found. Clinical, laboratory and imaging biomarker findings in EUA patients are shown in Table II.

At six months of follow-up, 17/70 EUA patients evolved into ERA (EULAR/

Table II. Serological, clinical and imaging biomarkers of patients with early undifferentiated arthritis (EUA).

	Mean ± SEM	95% confidence interval	Percentage (calculated with cut-off for laboratory tests)
Erythrocyte sedimentation rate (ESR) mm/h	21.04 ± 0.91	17.22-24.87	42.85% (>20 mm/h)
C-reactive protein (CRP) mg/dL	0.33 ± 0.36	0.61-2.05	38.57% (>0.5 mg/dL)
Rheumatoid factor IgM U/mL	25 ± 2.4	20.24-29.85	12.3% (>20 U/mL)
Anticitrullinated antibodies (ACPA) U/mL	13.39 ± 5.4	2.5-24.2	6% (>5 U/mL)
Serum calprotectin mcg/mL	31.43 ± 6.05	19.31-43.55	60% (>1.7 mcg/mL)
HLA-DRB1*11-positive	-	-	45%
Antinuclear antibodies (ANA)-positive	-	-	24.5%*
Tumour necrosis factor (TNF)-α pg/mL	15.97 ± 0.24	15.48-16.45	7.69% (>15.6 pg/mL)
Interleukin-6 pg/mL	6.48 ± 2.01	2.46-10	20% (>3 pg/mL)
CDAI 0-76	17.79 ± 0.91	15.97-19.6	-
Pain at clinical examination NRS 0-10	5.67 ± 0.36	4.95-6.4	-
Fatigue NRS 0-10	5.14 ± 0.33	4.47-5.81	-
Stiffness: NRS 0-10;	5.77 ± 0.36;	5.04-6.49;	
duration in minutes	52.29 ± 4.49	43.32-61.25	-
Synovitis maximal Power Doppler 0-3	1.44 ± 0.11	1.22-1.66	-
Tenosynovitis/ peritendinitis maximal Power Doppler 0-3	0.81 ± 0.11	0.58-1.04	-
Erosion at Ultrasound 0-3	0.37 ± 0.08	0.19-0.54	22.85%
SENS x-ray, 0-56	0.3 ± 0.1	0.09-0.5	12.85%

*Out of 17/70 EUA patients (24.5%) ANA-positive at baseline, only one patient was SSA/Ro-positive (ENA analysis) and anti-dsDNA-positive (high titre), but did not manifest complete systemic lupus erythematosus clinical expression at follow-up.
Values are expressed as mean±SEM, lower and upper 95% confidence interval for absolute parameters and percentage for binary parameters. Percentages are calculated with cut-off for laboratory tests (indicated) and for presence/absence of erosions at imaging.

ACR 2010 criteria) with progression of SENS from 0.23±0.66 to 1.29±2.31. There were no differences in AIMS parameters between the 17 patients reclassified as ERA and the remaining 53 EUA patients (Table I).

In EUA, mobility impairment correlated with tender and swollen joint counts (p=0.04 and p=0.02, respectively) and was higher in ESR-positive patients (p=0.04). Physical activity impairment correlated with tender and swollen joint counts (p=0.03 and p=0.006, respectively), fatigue NRS (p=0.0001), stiffness NRS (p=0.01), CDAI (p=0.01), PD synovitis at US (p=0.02), ESR (p=0.03), serum TNF-α (p=0.007), and was higher in TNF-α-positive than in TNF-α-negative patients (p=0.01). ADL impairment of patients older than 50 years correlated with CRP levels (p=0.01), and was lower in HLA-DRB1*11-positive subjects (p=0.006) (Fig. 1). Pain correlated with tender joint count (p=0.002), stiffness NRS (p=0.009) and duration (p=0.01), as well as with CDAI (p=0.01). Depression correlated with tender and swollen joint counts (p=0.04 and p=0.01, respectively), CDAI (p=0.009), pain at clinical examination NRS (p=0.04), PD synovitis at US (p=0.007) and ESR levels (p=0.022), and was lower in HLA-DRB1*11-positive patients (p=0.0004) (Fig. 1). Anxiety was higher in serum calprotectin-positive (p=0.02) and lower in HLA-DRB1*11-positive patients (p=0.01) (Fig. 1). Dexterity, household and social activities did not correlate significantly with any biomarkers.

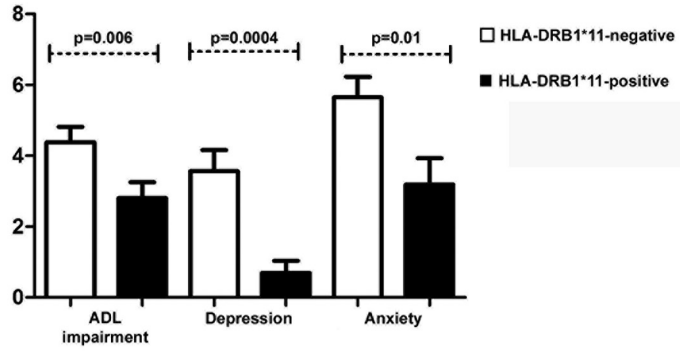

Fig. 1. Lower levels of activities of daily living (ADL) impairment, depression and anxiety in HLA-DRB1*11-positive compared with HLA-DRB1*11-negative early undifferentiated arthritis (EUA) patients.

Discussion

In the current study, impairment and disability subscales resulted high in patients with EUA with no significant differences in respect to either established RA or ERA, which is different from the findings of Soderlin *et al*. (1) reporting higher levels of dexterity, household, ADL impairment and pain in ERA patients than in other early arthritides along with similar grades of mobility, physical and social activities, depression and anxiety. Furthermore, in our EUA patients, mobility, physical activity, ADL impairment, pain, depression and anxiety correlated significantly with clinical (pain, fatigue, stiffness, CDAI), US (PD synovitis) and serological (ESR, TNF-α, calprotectin, HLA-DRB1*11) markers of disease activity, thus demonstrating the close relationship of impairment and disability with inflammation in early disease. Only pain correlated with clinical scores (joint count, CDAI, stiffness) but not with other biomarkers, which may be explained by the limits of subjective coping of patients regardless of the real

disease state. Among the different hypotheses on possible different aetiologies, discordance of pain intensity and disease activity with abnormality of central pain pathways was addressed by Challa *et al*. (10) as the most probable cause. In addition, the correlation of PD synovitis with both physical activity impairment and depression, but not with pain, that we found in EUA patients might confirm the discordance between the perception of patients and real inflammation demonstrated by previous data in RA patients on US remission related to good quality life parameters (11), but not to tenderness improvement (12).

Laboratory parameters, such as serum TNF-α, calprotectin and HLA-DRB1*11, had few previous evidence of association with quality of life parameters in arthritis. In particular, the implication of TNF-α in the response to exercise and muscle catabolism, as revealed by genetic polymorphism studies (13, 14), might suggest its possible influence on physical activity impairment. Serum calprotectin, known as predictor of therapeutic responses in RA, is also upregulated in microglia of schizophrenia and influences dendritic plasticity (15, 16), which may be in line with the higher anxiety found in our calprotectin-positive EUA patients. In our EUA patients, even depression correlated with ESR, clinical scores and PD synovitis, suggesting that mood disorders in early arthritis might be a consequence of inflammation because of the influence of microglia-released cytokines on neuronal impairment (17, 18). Finally, HLA-DRB1*11, which is one of the major gene determinants of disease susceptibility risk, severity and mortality in RA (19, 20), surprisingly seemed protective for depression, anxiety and ADL impairment in our limited cohort of EUA patients. These results might suggest that the "arthritogenic peptide hypothesis" of HLA-DRB1*11 is likely not the univocal mechanism responsible for its immunological implication in early arthritis (21), and that genetic predisposition might influence other disease aspects usually less considered.

In conclusion, in our EUA cohort impairment of mobility, physical activities, anxiety and depression displayed a significant correlation with both new and old inflammatory biomarkers of arthritis, while pain correlated only with clinical evaluation. HLA-DRB1*11 might be protective for ADL impairment, depression and anxiety.

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