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Power-Doppler perfusion phenotype in RA patients is dependent on anti-citrullinated peptide antibody status, not on rheumatoid factor

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Abstract

It is not known whether there are any consistent non-serological differences between seropositive and seronegative rheumatoid arthritis, and if any, whether they depend upon rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA), or both. In a pilot study, we showed that the two forms could be differentiated using power-Doppler sonography (PDS), and that the difference is ACPA dependent. This extended study explored whether the previous findings could be confirmed. 103 patients 51 ACPA positive (ACPA+), 52 ACPA negative (ACPA−) with active wrist arthritis were examined using PDS. By means of a temporal image series, pulsatility was evaluated over a 3–5-s period, maximum and minimum perfusion signal were determined using a computer program counting the number of coloured pixels for each frame. Maxima (P_{max}) and minima (P_{min}) were determined, and the standardized peak-to-peak amplitude sA was calculated ($sA = (P_{max} - P_{min})/P_{max}$). This parameter was then compared for ACPA + and ACPA- patients. In addition, a multivariate regression was performed, to determine which factors influence sA. sA differed significantly between ACPA + and ACPA- patients [20% (13–26) vs. 41% (32–57), $p < 0.0001$]. In the multivariate analysis, age ($t = 2.5$, $p = 0.02$) and ACPA status ($t = -4.8$, $p < 0.0001$) were independent predictors of sA. PDS perfusion patterns are different in seropositive and seronegative RA. The difference appears to be ACPA, not RF dependent. This suggests that the underlying pathophysiological process is different in ACPA-positive and ACPA-negative RA.

Keywords Power-Doppler sonography · ACPA-negative RA · Perfusion pattern

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Introduction

Rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) play an important role in the diagnosis [1] and risk stratification [2] of rheumatoid arthritis (RA). With the discovery of further arthritis-related peptides, the definition of seronegative RA has developed over time, and might change further [3]. Due to the differences in prognosis [4], therapeutic response [5, 6], and genetic predisposition [7], it has been postulated that there exists a separate, distinct disease entity within the seronegative RA collective [8], whereas other studies indicate that seronegative RA patients form a relatively homogeneous group [9].

If the two forms are indeed etiologically different, it must be assumed that the clinical phenotypes differ as well. Some features have been described, such as the polymyalgiform prodromal phase of late-onset (seronegative) RA [10], the predominant affection of the feet in seropositive RA [11], and the different patterns of radiological damage [12]. None

of these findings are conclusive, and only the X-ray observation quantifiable, though not practicable in a clinical setting.

Another unsolved question concerning 'seronegative RA' is which parameter defines the seropositive phenotype: ACPA, RF or both. The current classification criteria [13] do not differentiate in this respect; currently, 'seropositive RA' generally means 'either/or'. ACPA is known to be more specific than RF [14], RF seems only to predict the severity of disease in ACPA-positive patients, whereas it does not appear to play a significant role in ACPA-negative patients [15].

This is not merely an academical question; if only one of the serological factors (e.g., ACPA) is the real determinant for the RA phenotype, and the underlying pathological mechanisms of disease are different in the two forms, then the presence of both ACPA-positive and -negative patients in a study would constitute an important, unrecognized confounder.

In a pilot study [16], we described that it was possible to differentiate between seropositive and seronegative RA phenotypes using power-Doppler sonography (PDS) of the wrists. The results suggested that the phenotypical difference was dependent on ACPA, not RF status. The current study is an extension of the pilot study, aiming to explore these findings further, and investigate the significance of ACPA and RF for PD perfusion patterns.

Methods and materials

Patients

Patients with RA fulfilling the 1987 ACR criteria [17], and with sonographically active wrist synovitis (PDS 2 or 3 [18]) were successively recruited from one tertiary (University clinic Würzburg, Germany) and one secondary (Med I Bayern Ost, Burghausen, Germany) rheumatological centre. As in the pilot study [14], the 1987 criteria were chosen for being less weighted towards serological status than the 2010 ACR/EULAR criteria [13]. Patient data from the pilot study were included in the current study.

The study was approved by the ethics committee of the University of Würzburg; the examination was conducted according to the principles of the declaration of Helsinki, and written informed consent was obtained from all the patients.

Sonography

Ultrasound images were obtained using either an Esaote Mylab 60 or an Esaote Mylab 6 system with a linear 4–13 MHz transducer (Esaote SpA, Genoa, Italy). Doppler signals were detected with a pulse repetition frequency of 1 kHz.

A longitudinal scan of the dorsal wrist was performed and the point of maximal perfusion determined. In this area, an image series comprising several oscillations (3–7 s) between maximum (P_{max}) and minimum (P_{min}) perfusion as estimated by the examiner was obtained. PD sensitivity was set at submaximum levels, to avoid artefacts distorting the results. In patients with bilateral wrist arthritis, an image series was made from the joint with the highest maximum perfusion (P_{max}) as decided by the examiner; only one joint per patient was evaluated.

Serological tests

ACPA were measured using the EliA CCP Well (Phadia AB, Uppsala, Sweden) or ECLIA Roche (Roche Diagnostics GmbH, Mannheim, Germany). RF was measured using the RF-II test (Roche Diagnostics GmbH, Mannheim, Germany) or nephelometry, respectively. Cutoff values were provided by the local laboratory.

Data analysis

All data analysis procedures were performed by a study group member blinded towards the clinical and serological data.

The images were prepared for analysis using in-house developed software written in MATLAB (The MathWorks, Natick, MA). The algorithm was initialized using the DICOM image series obtained from the sonographical examinations described above. Perfusion (P) was measured for each frame by automatically counting the number of coloured pixels. A region of interest (ROI) was selected, and the local maxima and minima for P, i.e., the highest and lowest number of coloured pixels for each cycle, were labelled P_{max} and P_{min}, respectively. For further analysis, the average of the final two P_{max} and P_{min} values was calculated for each image series.

The peak-to-peak PDS amplitude, A, was calculated by subtracting P_{min} from the adjacent P_{max}. This was then standardized by dividing the resulting amplitude by P_{max}, yielding $sA = A/P_{max}$ (%). sA is the key parameter for our study.

Statistical analysis

Statistical analysis was conducted using Microsoft Excel (Microsoft Corp. Redmond, WA, USA), GraphPad Prism 5.0 (GraphPad Software Inc., La Jolla, CA, USA), and R Core Team (2018). (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

We performed a multivariate regression against the standardized peak-to-peak amplitude sA for the parameters age,

disease duration, ACPA status, RF status, DAS 28 and PD grading. In addition to the full model (fm), we examined the data using a model-choice strategy (mc), in which non-significant factors were deleted iteratively until only significant factors remained. From the resulting set of nested models, the optimal model is identified by the Likelihood Ratio Test (LRT). The results of both procedures (fm and mc) were compared to test for internal consistency. The fm results were shown as a Forest plot.

To examine any interactions between terms (such as RF and ACPA), we also compared sA for different sets of patients: ACPA-positive and -negative, and RF-positive and -negative patients were compared separately (ACPA + and ACPA −, and RF + and RF-, respectively). Median sA was also determined for ACPA-negative/RF-positive (ACPA-RF +) and ACPA-positive/RF- negative (ACPA + RF −) patients in a separate analysis. RF-positive patients were then compared according to ACPA status (RF + ACPA + vs. RF + ACPA −).

Groups were compared using the non-parametric, double-tailed Mann–Whitney test. p values < 0.05 were considered statistically significant.

In the pilot study [16], we found a difference in correlation coefficients between P_{min} and P_{max} between ACPA − and ACPA + patients. This analysis was repeated in this study, using Spearman's rho test. Finally, ROC curves were created for ACPA and RF vs. sA, to calculate the sensitivity and specificity of sA to discriminate between ACPA-positive and -negative, and RF-positive and -negative patients, respectively.

Results

A total of 103 patients were recruited from both centres. 51 were ACPA positive, 52 ACPA negative. The demographic and disease-specific data are shown in Table 1. Subgroup data are shown in Table 2. All data are presented as median and interquartile range (IQR).

There was no difference in disease activity between ACPA-positive and -negative patients as measured by DAS 28 (4.2 (3.0–5.0) vs. 4.5 (3.8–5.2); $p > 0.5$).

Age (57 (48–67) vs. 70 (62–79) years; $p < 0.0001$) and disease duration (13 (4–19) vs. 6 (< 1–13) years; $p = 0.0019$) were significantly different between ACPA + and ACPA − patients.

sA differed significantly between ACPA + and ACPA − [20% (13–26) vs. 41% (32–57); $p < 0.0001$] (Fig. 1), and between RF + and RF − [24% (15–32) vs. 40% (32–50); $p < 0.0001$] patients.

In the total cohort, age correlated with sA ($r = 0.54$, $p < 0.0001$). There was no significant correlation between sA and disease duration ($r = -0.17$, $p = 0.07$) or sA and DAS28 ($r = 0.08$, $p = 0.46$).

Table 1 Overall patient characteristics. All data given as median (interquartile range)

Parameter	ACPA+	ACPA −	p value
Patients (n)	51	52	n.s
Sex (m:f)	15/36	17/35	n.s
Age (years)	57 (48–67)	70 (62–79)	< 0.0001
Disease duration (years)	13 (4–19)	6 (0–13)	0.0019
DAS 28	4.2(3.0–5.0)	4.5(3.8–5.2)	n.s
RF positive (> ULN) (n)	49	17	< 0.0001
RF high positive (> 3 × ULN) (n)	35	6	< 0.0001
PD 3rd Grade	14	3	< 0.01
sA (%)	20 (13–26)	41 (32–57)	< 0.0001

sA Standardized peak-to-peak amplitude (amplitude/P_{max})

Examining RF-positive patients only, sA differed significantly between ACPA + RF+ ($n = 49$) and ACPA-RF + patients ($n = 17$): 20% (13–26) vs. 41% (28–58) (Fig. 2). For ACPA + RF − patients ($n = 2$), median sA was 12% (range 11–12).

Both for ACPA-positive and ACPA-negative patients there was a significant correlation between P_{min} and P_{max} (ACPA +: $r = 0.97$; ACPA −: 0.84; both $p < 0.0001$) (Fig. 3a, b).

The ROC curve for ACPA (Fig. 4a) yielded an AUC of 0.91, whereas the AUC for RF (Fig. 4b) was < 0.5.

In the multivariate analysis, both the fm (full model) and the mc (model choice) strategy identified age (fm: $t = 2.46$, $p = 0.02$; mc: $t = 2.63$, $p = 0.01$) and ACPA status (fm: $t = -4.84$, $p < 0.0001$; mc: $t = -6.42$, $p < 0.0001$) as independent predictors of sA. RF status, DAS 28 and PD grading had no statistically significant influence. A Forest plot of the fm multivariate regression is shown in Fig. 5.

Discussion

This study shows that power-Doppler sonography of the wrists is capable of distinguishing reliably between seropositive and seronegative RA, and confirms the results from the pilot project [16]. To our knowledge, this is the first consistent, real-time, quantifiable, non-serologic discriminant between seropositive and seronegative RA.

The multivariate analysis seems to confirm the assumption from the pilot study that ACPA is the defining parameter for determining sA phenotype. The similarities in pattern between ACPA-RF + and ACPA-RF − patients support this theory. The two ACPA-positive, RF-negative patients displayed a low-amplitude, 'seropositive' pattern.

Table 2 Subgroup characteristics

	ACPA + RF +	ACPA + RF −	ACPA-RF +	ACPA-RF −	RF +	RF −
Patients (*n*)	49	2	17	35	66	37
Sex (m/f)	17/32	0/2	6/11	11/24	23/43	11/26
Age (years)	58 (50–67)	38 (29–47)	69 (66–80)	70 (62–78)	60 (53–69)	69 (61–78)
Disease duration (years)	13 (4–19)	7 (4–9)	12 (< 1–16)	6 (< 1–12)	12 (3–18)	6 (< 1–11)
DAS 28	4.6 (3.3–5.1)	4.4 (4.3–4.4)	4.6 (4.3–5.4)	4.4 (3.6-5.0)	4.6 (3.5–5.2)	4.4 (3.7–4.9)
RF positive (> ULN) (*n*)	49	0	17	0	66	0
RF high positive (> 3 × ULN) (*n*)	35	0	6	0	41	0
PD 3rd Grade (*n*)	13	1	0	3	13	4
sA (%)	20 (13–26)	12 (11–12)	41 (27–61)	40 (33–51)	24 (14–32)	40 (33–48)

All data given as median (interquartile range)

sA Standardized peak-to-peak amplitude (amplitude/P_{max})

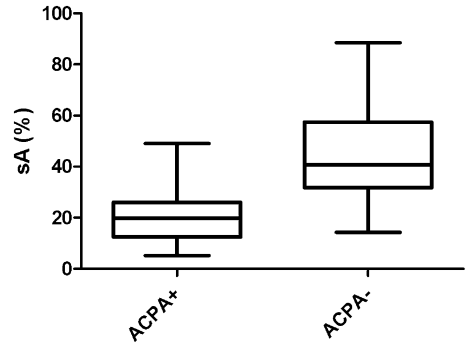

Fig. 1 Comparison of sA between ACPA-positive (ACPA+) vs. ACPA-negative (ACPA −) patients

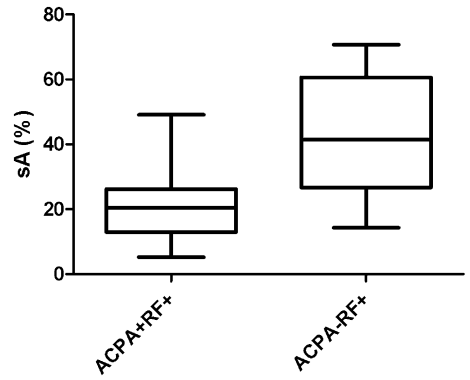

Fig. 2 Comparison of sA in RF-positive patients: ACPA-positive (ACPA + RF +) vs. ACPA-negative (ACPA-RF +) patients

The discriminating parameter is the standardized, or relative, peak-to-peak amplitude. This parameter is less dependent on the scanner setting than absolute pixel measurements or PD grading, for the observer sA is represented by the 'pulsatility' of the signal. In ACPA-positive patients, the pulsations are less pronounced, resulting in a 'shimmering' appearance, whereas in ACPA-negative patients, the pulsation is stronger, and the PD signal 'throbs'. Examples are provided online as supplementary material.

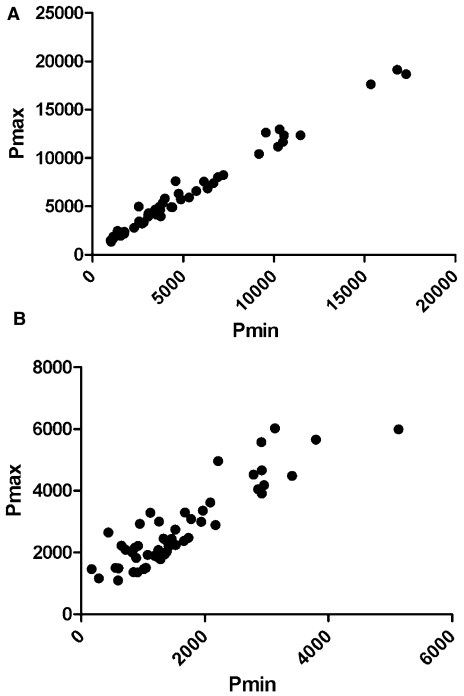

Fig. 3 **a** Correlation between P_{max} and P_{min} in ACPA-positive patients ($r = 0.97$). **b** Correlation between P_{max} and P_{min} in ACPA-negative patients ($r = 0.83$)

There is no final explanation for the observed differences, but it seems reasonable to assume that they arise through the involvement of different kinds of vessels. The 'throbbing' of ACPA-negative RA suggests the involvement of arterioles. This notion is supported by the relatively poor correlation between P_{min} and P_{max} in these patients (0.84 in ACPA-negative, 0.97 in ACPA-positive patients), which could be explained by the high-velocity, non-laminar blood

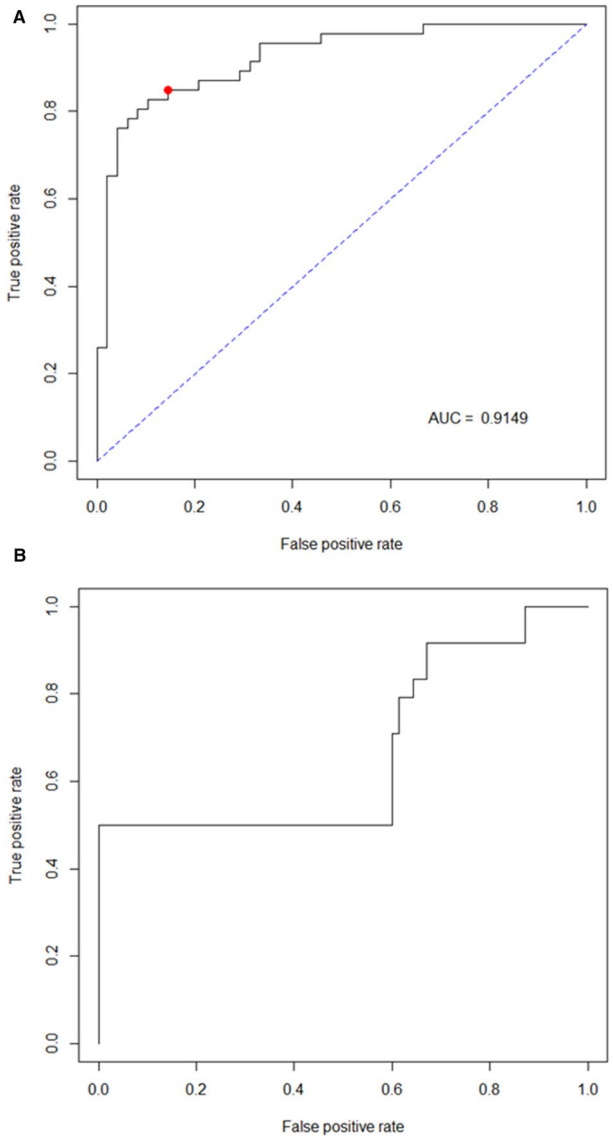

Fig. 4 **a** ROC curve for ACPA predicting sA (AUC = 0.91). **b** ROC curve for RF predicting sA (AUC < 0.5)

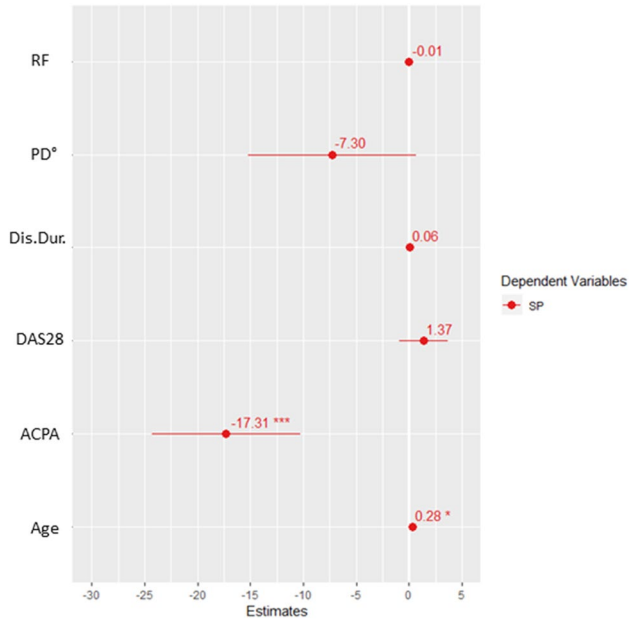

Fig. 5 Forest plot for fm multivariate regression. *RF*: rheumatoid factor; *PD* Power-Doppler grading; *Dis.Dur* disease duration, *ACPA* anti-citrullinated peptide antibody status

flow in such vessels, and the elasticity of the arteriolar wall. Conversely, the PDS signals in ACPA-positive RA, with their comparative lack of pulsatility, suggest a highly laminar flow originating in the capillary system. Potentially, the differences may reflect different cytokine profiles, e.g., tissue VEGF expression. Further research into this question is necessary.

These findings do not diminish the prognostic value of RF for risk stratification in ACPA-positive RA [2], and the nosological and taxonomical contribution of the rheumatoid factor to our field of medicine is indisputable [19]. However, if ACPA-negative, RF-positive RA displays the same phenotype as the double-negative patients, and RF has no prognostic value in these patients [15], it follows that the parameter is clinically irrelevant in ACPA-negative patients, and that its continued inclusion in the diagnostic criteria may have to be reconsidered.

A potential bias concerning the evaluation of RF in ACPA-negative patients is the difference in age between ACPA-positive and -negative patients; the ACPA-negative patients are significantly older. It is well known that RF positivity is relatively common in the elderly; a prevalence of 30% was reported in a collective aged similarly to our ACPA-negative group [20]. In our study, 17/52 ACPA-negative patients (33%) were RF positive, and only 6/52 (12%) were highly positive (> 3 × ULN). Hence, RF prevalence in our ACPA-negative RA patients was not higher than would be expected in an age-matched healthy control group—arguably, one could even have expected the prevalence to be higher in a patient collective with a chronic, inflammatory disease. This finding supports the notion that the presence of RF in ACPA-negative RA patients is a coincidence, not a trait of the disease itself. In comparison, 49/51 (96%) ACPA-positive patients were RF positive, and 35/51 (69%) were highly positive. The significant age difference between ACPA-positive and ACPA-negative patients might have contributed to age being a significant factor in the multivariate regression.

It is important to stress that the significance of our study does not lie in its ability to predict serologic status; a sonographic examination is more time consuming, less reliable, and probably no less costly than a laboratory test, at least if one considers the indirect costs. Rather, the study should

be interpreted as an argument that the relevant serological discriminant between 'seropositive' and 'seronegative' RA is not RF, nor RF and/or ACPA, but ACPA alone. In addition, the different amplitudes of ACPA-positive and ACPA-negative RA support the notion that the two forms are different entities. This potential confounding factor should be considered when designing new diagnostic or therapeutic studies. In addition, considering the delay in diagnosis for ACPA-negative RA patients [21], and the nosological difference between the two forms, it could be argued that the classification criteria for ACPA-negative RA should be revised.

The size and scope of the study was relatively limited, especially for some of the sub-groups. Ideally, further studies with a larger scope should be conducted to confirm the results, and a longitudinal study to show that the findings are stable over time and with varying degrees of disease control. In addition, it should be evaluated whether the differences can be observed in other joints than the wrist.

Another weakness in this study is the lack of data on CRP and ESR tests. It is conceivable that the level of inflammatory activity may influence tissue perfusion and thus confound our results. On the other hand, sA was independent of DAS 28, which is an established parameter for measuring disease activity.

There is one possible clinical utility for our findings, namely for differential diagnosis. The pulsatile pattern seems to be relatively specific for ACPA-negative RA sensu stricto, whereas our experience indicates that other etiologies such as articular infection, or osteoarthritis (e.g., as a consequence of scapholunar dissociation) generally display a less pulsatile perfusion pattern, similar to ACPA-positive RA. Potentially, the perfusion pattern could be used to identify patients in whom the 'seronegative RA' diagnosis should be doubted, and other pathogeneses considered. Regarding other defined arthritis syndromes, such as psoriatic arthritis, we have made no observations up until the present.

In conclusion, this study finds that ACPA-positive and ACPA-negative RA can be differentiated reliably using power-Doppler sonography, suggesting different pathophysiological or even nosological processes. Our findings also suggest that RF is not helpful for determining the RA phenotype.

The significance of these results should not be overstated, and further research into this and other aspects of ACPA-negative RA is necessary, both in isolation and in comparison with ACPA-positive disease. However, we would argue that our findings justify such a research effort.

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Author contributions OG: underlying observation, study design, patient recruitment, sonographic examination, data analysis, data interpretation, and first draft; MF: patient recruitment, sonographic examination, and draft revision; TW: data preparation, data post-processing, and draft revision; ECS: study design, patient recruitment, sonographic examination, data interpretation, and draft revision.

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Compliance with ethical standards

Conflict of interest OG: speaker's fees from Abbvie, Chugai, Janssen-Cilag, Novartis, and Sanofi. Grants from Abbvie, Chugai, Janssen-Cilag, Lilly, Novartis and Roche. Advisory board participation for Novartis. All outside the submitted work. MF: personal Fees from Abbvie, Chugai, Janssen-Cilag MSD, Pfizer, Roche and UCB. All outside the submitted work. TW: research grant from Siemens Healthcare. Outside the submitted work. ECS: speaker's fees from Abbvie, Chugai, Jansen-Cilag, Lilly, Novartis and Shire. Grants from Abbvie, Celgene, Chugai, Novartis and Shire. All outside the submitted work.

Ethics approval Final approval by the ethics committee of the University of Würzburg, Würzburg, Germany 20.07.2018 (Protocol Number 22/18). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Data sharing No application was submitted to the ethics commission of the University of Würzburg for permission to share the obtained data. Hence, the data cannot be made available for further analysis.

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