The prognostic value of IgA anti-citrullinated protein antibodies and rheumatoid factor in an early arthritis population with a treat-to-target approach

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RESEARCH

The prognostic value of IgA anti-citrullinated protein antibodies and rheumatoid factor in an early arthritis population with a treat-to-target approach

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Abstract
The mucosal origin hypothesis of rheumatoid arthritis has renewed the interest in IgA autoantibodies, but their added value over IgG anti-citrullinated protein antibody (ACPA) and IgM rheumatoid factor (RF) for modern treatment outcomes remains unknown. We aimed to investigate the prognostic value of IgA-ACPA and IgA-RF for treatment outcomes in an early arthritis population. IgA-ACPA/RF isotypes were measured in baseline sera from 480 inflammatory arthritis (IA) patients, who were included in the treatment in the Rotterdam Early Arthritis Cohort trial (tREACH). The tREACH trial was a multicentre, stratified, single-blinded trial with a treat-to-target approach. The prognostic value of IgA-ACPA/RF was determined by evaluating differences in (1) quick-attained (< 6 months after diagnosis) and persistent remission rates, (2) DMARD-free remission and (3) biological use between IA patients with and without IgA-ACPA/RF over 3 years of follow-up. IgA-ACPA was present in 23% of patients and overlapped with IgG-ACPA positivity in 94%. Similarly, IgA-RF overlapped with IgM-RF in 90% of patients. IgA-ACPA positivity was associated with lower DFR rates and more biological use, but this effect was largely mediated by the presence of IgG-ACPA, since this effect disappeared after stratification for IgG-ACPA (HR 0.6, 95%CI 0.2-1.6 for DFR). No differences were observed in 'quick-attained and persistent remission' rates and for IgA-RF. Their seems to be no additional value of IgA-ACPA and IgA-RF for modern, long-term clinical outcomes. The effects of IgA-ACPA seen in our study are largely mediated by the presence of IgG-ACPA. Based on these results, there is no rationale for measuring these isotypes in daily practice.

Keywords IgA autoantibodies · Rheumatoid arthritis · Anti-citrullinated protein antibody · DMARD-free remission

Introduction

The 2022 EULAR research agenda for rheumatoid arthritis (RA) management states that new biomarkers are needed to stratify RA patients and to predict therapeutic response or lack of response [1]. It also emphasises the importance of identification of disease endophenotypes, which is the first step towards personalised medicine [1]. RA patients can be stratified into disease endophenotypes by autoantibodies. IgG anti-citrullinated protein antibody (ACPA) and IgM rheumatoid factor (RF) positivity are used in current RA guidelines as poor prognostic factors for second-line treatment decisions and thus stratify patients into autoantibody positive and negative RA [1]. IgA isotypes of ACPA and RF may help further differentiate RA into endophenotypes.

IgA ACPA and RF have gained renewed interest in the context of the mucosal origin hypothesis in the pathogenesis of RA [2]. Mucosal surfaces have been proposed as the site of initial triggering events, especially in autoantibody positive RA. In this hypothesis, chronic mucosal inflammation transitions to systemic autoimmune disease with loss of the mucosal barrier leading to a systemic instead of local autoantibody response [3]. IgA is the main immunoglobulin isotype produced at mucosal surfaces. If systemically

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present at high levels, immune complexes can be formed which can damage tissues, including joints [4]. On the other hand, IgA antibodies can be considered anti-inflammatory as they are not strong complement activators and are resistant to proteolytic degradation [3]. Since IgA autoantibodies could thus have opposing pro- and anti-inflammatory roles, their presence could be both positively and negatively associated with disease activity, damage and other treatment outcomes in RA.

In RA, systemic IgA-ACPA and IgA-RF predominantly co-occur with IgG ACPA and IgM RF, although IgA ACPA and IgA RF have also been reported in a proportion of IgG ACPA and IgM RF negative RA patients [5–7]. Two studies looked into the value of IgA ACPA in addition to IgG ACPA. One reported higher disease activity over the course of 3 years in IgA ACPA positive patients, a result that did not remain in the IgG ACPA positive patients only [8]. The other study reported a non-significant higher flare risk in double positive (IgA and IgG ACPA) patients compared to single positive or negative patients [6]. Furthermore, three studies reported on secretory IgA ACPA, which is dimeric instead of monomeric circulating IgA. One investigated the value of secretory IgA ACPA in RA and did not find an association with disease activity or erosive disease [9]. The other did find an association between salivary IgA ACPA and disease activity, but not with erosive disease [7]. The third study found an inverse association between salivary IgA ACPA and erosive disease [10]. Altogether, previous data suggest that IgA ACPA could contribute to worse RA outcomes, but results are inconclusive and the value over IgG ACPA is debatable.

Studies on the prognostic role of IgA-RF report an association of IgA RF with more active and erosive disease [11, 12]. Fortunately, erosive disease is less common nowadays and most studies on the prognostic value of IgA RF took place > 20 years ago. Nowadays, alternative treatment outcomes (as opposed to erosive disease) have become increasingly important, such as sustained remission and DMARD-free remission (DFR) [13]. Previous research already showed that autoantibody positive RA patients are less likely to achieve DFR and more often use biologicals [14–17]. Unfortunately, there is only one study that reported on DFR and other autoantibody isotypes, including IgA. The authors of this study concluded that a higher number of ACPA and RF autoantibody isotypes reduced the chance at achieving DFR [18]. However, this study did not focus on IgA specifically or independently from concomitant IgG presence. Thus, to our knowledge, there are no studies that investigated the added prognostic value of IgA ACPA and IgA RF for the abovementioned 'modern' treatment outcomes.

Therefore, to help unravel the current knowledge gap, we determined the added prognostic value of IgA ACPA and IgA RF by looking at the differences in (1) 'quick-attained and persistent remission' rates, (2) DFR rates and (3) biological use over a 3-year follow-up period between newly diagnosed inflammatory arthritis patients with and without IgA ACPA and IgA RF who were managed with a treat-to-target approach.

Methods

Study population

For this study, inflammatory arthritis (IA) patients who participated in the treatment in the Rotterdam Early Arthritis cohort trial (tREACH) and who had an available baseline serum sample were included [19, 20]. The tREACH was a multicentre, stratified, single-blinded randomised controlled trial. Inclusion criteria for the tREACH were (1) arthritis in ≥ 1 joint, (2) symptom duration < 1 year and (3) age > 18 years. Patients were stratified into 3 groups according to their risk of progressing to persistent arthritis, which was based on the prediction model of Visser [21]. Subsequently, patients were randomised to receive different initial treatment strategies. Patients received one of the following four initial treatment options: (1) triple DMARD therapy (methotrexate (MTX) + sulfasalazine (SASP) + hydroxychloroquine (HCQ) + glucocorticoid (GCs) bridging), (2) MTX with or without GC bridging therapy, (3) HCQ, (4) GC treatment or non-steroidal anti-inflammtory drugs (NSAIDs) (no DMARDs). The tREACH trial had a treat-to-target approach, aiming at low disease activity (DAS < 2.4). Treatment alterations could occur at each 3-monthly visit and treatment was intensified if DAS ≥ 2.4. Intensifications steps were as follows: (1) triple DMARD therapy (MTX + SASP + HCQ), (2) MTX + etanercept, (3) MTX + adalimumab and (4) MTX + abatacept. Medication was tapered if DAS < 1.6 at two consecutive visits. Medication was gradually discontinued, except for HCQ and naproxen, which were immediately stopped. In case of a flare (DAS ≥ 2.4) during tapering, treatment was restarted, according to the stage in the protocol. An extensive description of the study can be found elsewhere [19, 20].

Autoantibody measurements

At baseline, blood samples were obtained and serum was stored at − 80°. In the baseline sera, the presence of autoantibody isotypes IgG ACPA, IgA ACPA, IgM RF, and IgA RF was determined by automated fluorescence enzyme immunoassay (FEIA) using the Phadia250 EliA™ platform (Thermo Fisher Scientific, Freiburg, Germany), according to the manufacturer's instruction. These tests have been validated in a group of healthy control subjects by Thermo Fisher (see Supplemental Table S1 for frequency distributions in

healthy controls). Cut-offs for autoantibody positivity were employed according to the manufacturer's instruction. The cut-off levels for autoantibody isotype positivity were ≥ 7 U/ml for IgG ACPA, ≥ 7 U/ml for IgA ACPA, ≥ 3.5 IU/ml for IgM RF and ≥ 14 IU/ml for IgA RF.

Outcome measures

IgA ACPA and IgA RF positive patients were compared with IgA ACPA and IgA RF negative patients for 3 outcome measures: (1) the proportion of patients that quickly attained (within 6 months) remission (DAS < 1.6) and stayed in remission over a 2-year time period (i.e. 'quick-attained and persistent remission'), the most favourable outcome in the first years of RA treatment; (2) the proportion of patients that achieved DFR, defined as the absence of clinical synovitis (swollen joints at physical examination) and no DMARD use (including oral glucocorticoids) for ≥ 6 months, over the course of 3 years; and (3) the proportion of patients using a biological over the course of 3 years.

Statistical analysis

Statistical comparisons of baseline characteristics were made by Student's *t*-test, χ^2 test, Fisher's exact test, or Wilcoxon rank-sum test, when appropriate. Baseline characteristics from patients without data on DFR at 3 years—due to lost to follow-up (54%) and due to missing variables (10%)—did not differ (Supplemental Table S2). Differences in the proportion of patients achieving 'quick-attained and persistent remission' were analysed using logistic regression models. The probabilities of achieving DFR and biological use over the course of 3 years were visualised with Kaplan Meier curves. Patients that were lost to follow-up were censored. Subsequently, differences in the proportion of patients achieving DFR and using biologicals were analysed using Cox-proportional hazard models. Kaplan Meier curves and analyses were stratified for IgG ACPA and IgM RF, because DFR and biological usage rates are different for autoantibody positive and negative IA patients and because the presence of IgG ACPA and IgM RF influenced the initial treatment strategy, which was partly determined by the risk stratification based on the prediction model for persistent arthritis of Visser et al. [13, 17]. *p* values ≤ 0.05 were considered statistically significant. All statistical analyses were performed in STATA 17.

Results

Prevalence of IgA ACPA and IgA RF isotypes

Autoantibody isotypes were measured in baseline sera of 480 tREACH patients. A positive IgA ACPA titre was present in 22.7% of IA patients and most of them were also positive for IgG ACPA (overlap of 94%, Fig. 1). Positive IgA RF was present in 35.6% of IA patients, which overlapped with IgM RF in 90% of patients (Fig. 1). Only a few IA patients were solely positive for IgA ACPA or IgA RF (1% and 4%, respectively).

Study population

Baseline characteristics of the 480 included patients are stratified for IgA ACPA and RF presence or absence (Table 1). IgA isotype positive IA patients had higher disease activity and inflammatory markers at baseline compared

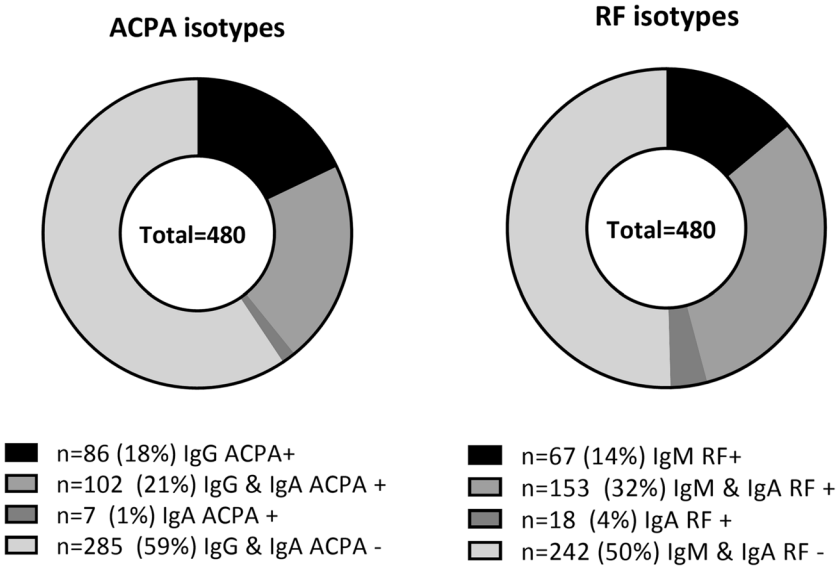

Fig. 1 Prevalence of ACPA and RF isotypes. Prevalence of ACPA and RF isotypes in 480 IA patients. Both IgA ACPA and IgA RF predominantly overlap with commonly measured isotypes (IgG ACPA and IgM RF, respectively). Abbreviations: ACPA, anti-citrullinated protein antibody; IA, inflammatory arthritis; RF, rheumatoid factor

Table 1 Baseline characteristics of included IA patients ($n=480$), stratified for IgA ACPA or RF presence or absence

	IgA ACPA +		IgA ACPA −		*p value*	IgA RF +		IgA RF −		*p value*
	$n=109$		$n=371$			$n=171$		$n=309$		
Gender, female, n (%)	67	(61)	252	(68)	*0.21*	110	(64)	209	(68)	*0.46*
Age, mean (sd)	55	(13)	52	(15)	*0.06*	54	(13)	52	(15)	*0.20*
Symptom duration (weeks), median (IQR)	22	(13–30)	21	(13–31)	*0.88*	21	(13–30)	21	(13–32)	*0.64*
DAS44, mean (sd)	3.3	(1)	3.0	(1)	*0.01*	3.3	(1)	3.0	(1)	*0.006*
Swollen joint count, median (IQR)	8	(4–12)	5	(2–9)	*< 0.001*	8	(4–12)	4	(2–8)	*< 0.001*
Tender joint count, median (IQR)	8	(3–14)	7	(3–13)	*0.71*	7	(3–14)	7	(4–13)	*0.96*
1987/2010 RA criteria, n (%)	101	(93)	234	(63)	*< 0.001*	158	(92)	177	(57)	*< 0.001*
CRP (mg/l), median (IQR)	10	(5–22)	6	(3–17)	*0.009*	9	(4–24)	6	(3–15)	*0.002*
ESR (mm/h), median (IQR)	25	(15–42)	16	(8–30)	*< 0.001*	24	(14–42)	15	(8–29)	*< 0.001*
IgG ACPA +, n (%)	102	(94)	86	(23)	*< 0.001*	149	(87)	39	(13)	*< 0.001*
*IgG ACPA level (IU/ml), median (IQR)**	340	(327–340)	96	(36–189)	*< 0.001*	327	(119–340)	175	(55–340)	*0.09*
IgM RF +, n (%)	99	(91)	121	(33)	*< 0.001*	153	(89)	67	(22)	*< 0.001*
*IgM RF level (IU/ml), median (IQR)***	81	(30–170)	23	(9–52)	*< 0.001*	63	(29–135)	10	(5–48)	*< 0.001*

ACPA anti-citrullinated protein antibody, *CRP* C-reactive protein, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *IA* inflammatory arthritis, *IQR* interquartile range, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *sd* standard deviation

*In IgG ACPA positive patients

**In IgM RF positive patients

to IgA isotype negative IA patients, both for IgA ACPA and IgA RF positivity.

Quick-persistent remission

Sixteen percent of IA patients achieved remission within 6 months that persisted over 2 years. These 'quick-attained and persistent' remission rates did not significantly differ between IgA ACPA positive and negative patients (OR 1.1 (95% CI 0.6–2.0), Fig. 2) and IgA RF positive and negative patients (OR 1.3 (95% CI 0.8–2.2), Fig. 2). Stratified analysis for commonly measured isotypes (IgG ACPA and IgM RF) showed similar results (Supplemental Fig. S1).

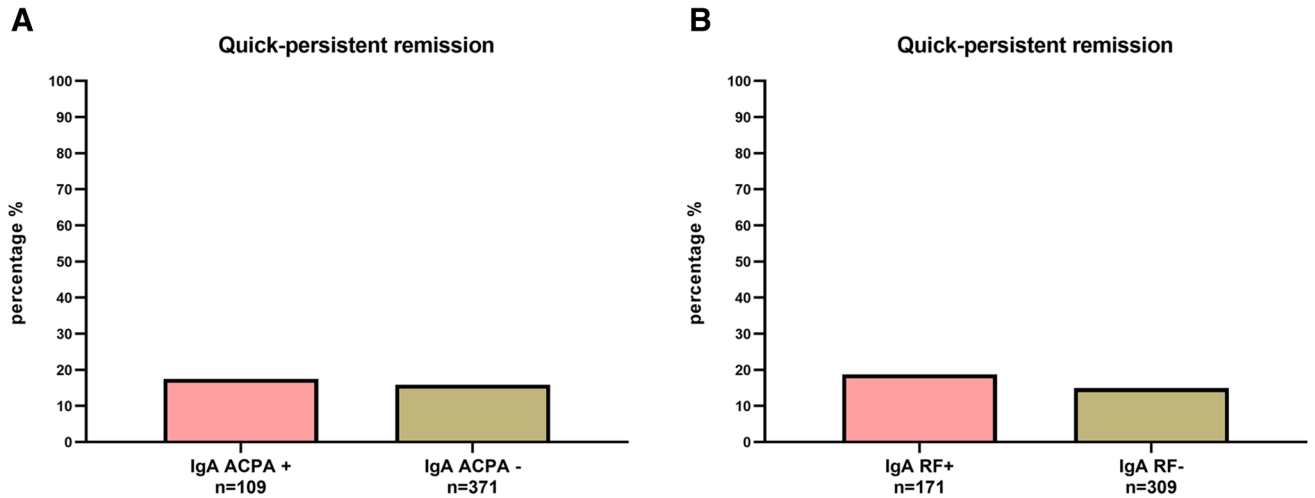

Fig. 2 Quick-persistent remission in IgA ACPA/RF positive versus IgA ACPA/RF negative patients. 'Quick-attained and persistent' remission rates in **A** IgA ACPA positive vs. negative patients and in **B** IgA RF positive vs. negative patients. 'Quick-attained and persistent' remission was defined as the proportion of patients that quickly attained (within 6 months) remission (DAS < 1.6) and stayed in remission until 2 years of follow-up. Data stratified for commonly measured isotypes (IgG ACPA and IgM RF) showed similar results (Supplemental Fig. S1). Abbreviations: ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor

IgA ACPA and the chance of DFR and biological use

IgA ACPA positive patients had a significantly lower chance at achieving DFR over 3 years compared to IgA ACPA negative patients (cumulative percentage 9.4% vs. 20.8%, HR 0.41, 95% CI 0.20–0.86, Fig. 3A). When adjusting for the effect of IgG ACPA, the analysis still revealed lower DFR rates for IgA ACPA positive patients compared to IgA ACPA negative patients, but this finding was not significant anymore (cumulative percentage 8.7% vs. 13.3%, HR 0.60, 95% CI 0.22–1.61, Fig. 3B). Furthermore, IgA ACPA positive patients had a significantly higher chance at biological use over 3 years compared to IgA ACPA negative patients (cumulative percentage 44.6% vs. 34.3%, HR 1.44, 95% CI 1.02–2.04, Fig. 3A). After adjustment for IgG ACPA positivity, biological use was still numerically higher in IgA ACPA positive patients, but this finding did not remain significant (cumulative percentage 44.7% vs. 37.8%, HR 1.24, 95% CI 0.77–1.98, Fig. 3B).

IgA RF and the chance of DFR and biological use

IgA RF positive patients had a non-significant lower chance at achieving DFR over 3 years compared to IgA RF negative patients (cumulative percentage 13.5% vs. 20.7%, HR 0.62, 95% CI 0.36–1.06, Fig. 4A). This numerical difference disappeared after taking IgM RF positivity into account (cumulative percentage 14.5% vs. 14.6%, HR 0.84, 95% CI 0.35–2.00, Fig. 4B). In addition, the chance of biological use was similar for IgA RF positive and IgA RF negative patients, both in the whole population (cumulative percentage 39.9% vs. 34.7%, HR 1.24, 95% CI 0.90–1.70, Fig. 4A) and after accounting for IgM RF positivity (cumulative percentage 40.4% vs. 42.7%, HR 0.96, 95% CI 0.61–1.51, Fig. 4B).

Discussion

In this study, we aimed to evaluate the prognostic value of the IgA autoantibody isotypes of ACPA and RF in an early arthritis population. We showed that positivity for both IgA ACPA and IgA RF almost completely overlapped with positivity for the commonly measured autoantibody isotypes IgG ACPA and IgM RF. The prognostic value of IgA ACPA and IgA RF was studied for the outcomes of 'quick-attained and persistent' remission rates, the probability of reaching DFR, and the probability of using a biological over the course of

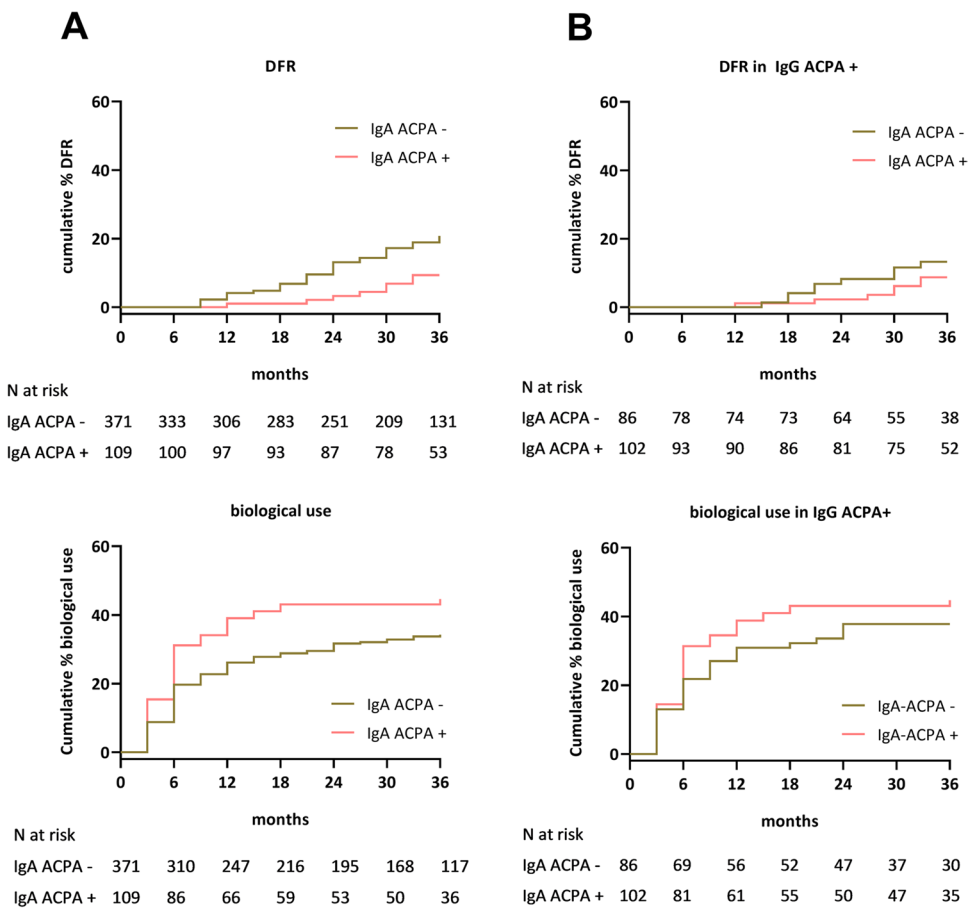

Fig. 3 DMARD-free remission and biological use in IgA ACPA positive vs. IgA ACPA negative patients. Kaplan Meier curves for achievement of DMARD-free remission and biological use over 36 months in **A** the whole population and in **B** IgG ACPA positive patients comparing IgA ACPA positive and IgA ACPA negative patients. Abbreviation: ACPA, anti-citrullinated protein antibody

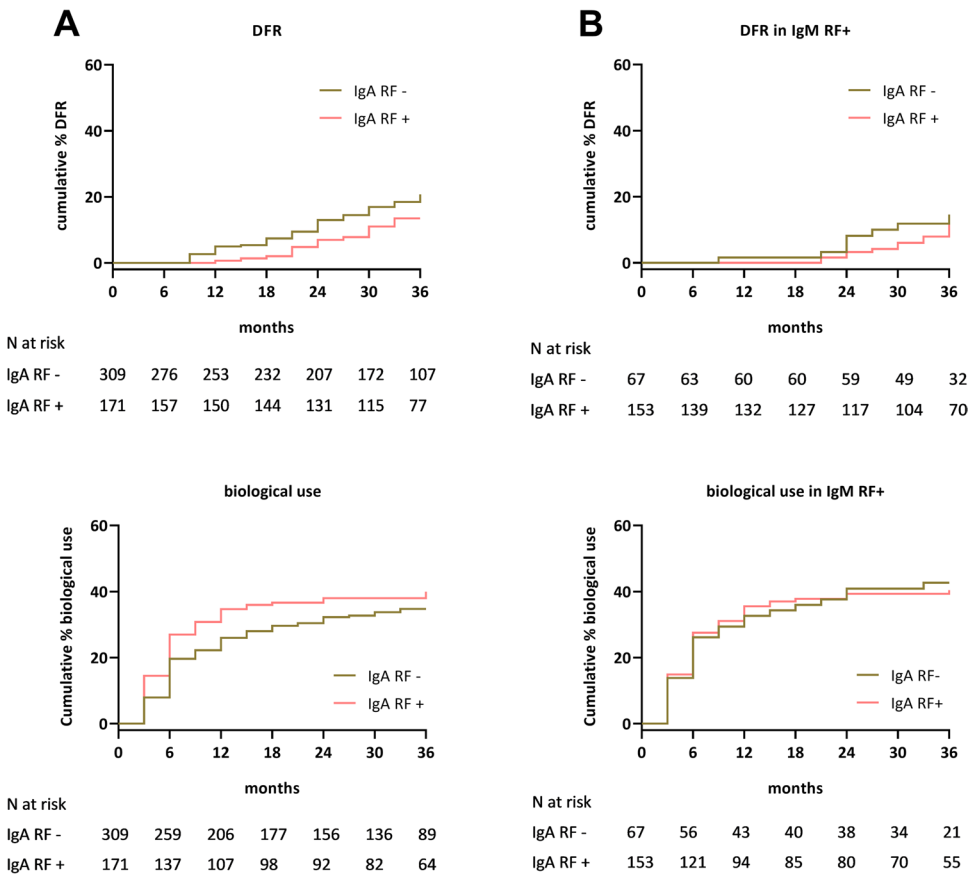

Fig. 4 DMARD-free remission and biological use in IgA RF positive vs. IgA RF negative patients. Kaplan Meier curves for achievement of DMARD-free remission and biological use over 36 months in **A** the whole population and in **B** IgM-RF positive patients comparing IgA RF positive and IgA RF negative patients. Abbreviation: RF, rheumatoid factor

3 years. Both IgA ACPA and IgA RF were not associated with 'quick-attained and persistent remission' rates. IgA-ACPA was significantly associated with DFR achievement and the risk of biological use over 3 years. However, most of this risk should be appointed to IgG-ACPA positivity in that group, since the same analysis in IgG-ACPA positive patients did not show a significant difference in DFR and biological use. For IgA RF, there was no significant difference between IgA RF positive and negative patients in achievement of DFR and risk of biological use.

Our finding that IgA isotypes have a large overlap with commonly measured isotypes is in line with previous studies. A previous study in early RA showed that the majority of IgA ACPA and/or IgA RF positive patients were also positive for IgG ACPA and/or IgM RF [22]. One study in early and established RA patients found that 5.2% of the IgG ACPA and IgM RF negative population was positive for IgA ACPA and/or IgA RF, which is similar to our data (1% IgA ACPA positivity and 4% IgM RF positivity) [5]. Another study found a 2.5–5.8% positivity for IgA RF in the IgM RF negative RA population [23]. Altogether, only a very small number of early arthritis patients without commonly measured autoantibodies are positive for IgA ACPA and IgA RF.

The measurement of IgA ACPA and IgA RF in a clinical setting is only relevant when they can provide prognostic information for RA patients for modern treatment outcomes and when they have added value over the commonly measured antibodies. Therefore, we studied the prognostic value of IgA ACPA and IgA RF for the outcomes of 'quick-attained and persistent' remission, DFR and biological use. Regarding ACPA, it is well known that the IgG isotype is of prognostic value [17, 24, 25]. Previous literature has shown that chances of achieving DFR are lower and the risk of biological use is higher in IgG ACPA positive patients compared to IgG ACPA negative patients [14, 24, 26]. Our results showed that IgA ACPA was associated with lower DFR rates and more biological use, but this was largely mediated by the known effect of IgG ACPA since most patients were also IgG-ACPA positive and when accounting for IgG ACPA positivity these differences mostly disappeared.

In our data, IgA RF was not associated with any of the aforementioned disease outcomes. Previous studies that investigated the relationship between IgA RF positivity and disease outcomes have shown that IgA RF positivity is associated with more active and erosive disease [11, 27–32]. However, most of these studies come from years when IgG ACPA was not yet known as the best predictive autoantibody for treatment outcomes in RA and, therefore, information on IgG ACPA in these studies is lacking [11, 28–32].

A more recent study that included information on ACPA also found that IgA-RF was a predictive factor for erosive disease, but also showed that IgG ACPA in combination with IgM RF and not IgA RF predicted erosive disease more accurate [33]. All aforementioned studies focused on erosive disease (and/or disease activity), which is a much less common feature of RA nowadays due to better treatment options. To our knowledge, the added value of IgA RF for modern treatment outcomes such as DFR and biological use has not been evaluated in past and current literature and we are the first to report on this.

Our study is relevant in the context of the mucosal origin hypothesis, in which IgA autoantibodies might play a role in triggering events that lead to RA [2, 3]. Based on our findings, we believe that a subgroup of patients with IgA autoantibodies and thus possibly a specific underlying trigger for their disease do not necessarily have a different prognosis compared to IgA negative patients. An initial disease trigger that in this case might be reflected by the presence of circulating IgA autoantibodies does not necessarily imply a different clinical course in a later disease stage. Nevertheless, reporting these results is important because clear markers for prognosis are still lacking and research aimed at finding prognostic biomarkers is needed for precision medicine [34]. Alternatively, circulating IgA ACPA does not unquestionably reflect an initial disease trigger at the mucosal site, since there is evidence that circulating IgA does not correlate with salivary IgA presence in RA [10]. Circulating IgA antibodies might be produced independently of mucosal IgA and reflect more of a general broad autoantibody profile caused by more humoral autoimmunity. The numerical difference in DFR and biological use in our data between IgA positive and negative patients in the IgG ACPA positive group could be a result of a stronger humoral autoimmunity and consequently lead to a more severe disease with worse outcomes. This is also in line with what Moel et al. reported, who showed that a broader autoantibody profile, possibly caused by more humoral immunity, is associated with worse treatment outcomes in early RA [18].

Limitations of the current study include the small number of events for DFR, which gave less power to find statistical significance for some numerical differences that we saw in the data. In addition, correcting for confounders was not possible due to the small number of events. However, the findings for biological use were concordant with the findings for DFR, and due to this consistency, we believe our results are valid. Secondly, the unstratified analyses might have been influenced not only by the concomitant presence of IgG ACPA and IgM RF but also by differences in the initial treatment strategy, since these were IgG ACPA and IgM RF dependent [21]. Thus, the effect of IgA ACPA on DFR and biological use might have been mediated not only by the presence of IgG ACPA but also by the initial treatment strategy. Moreover, there was a relatively high percentage of missing data (the highest being 64% for DFR at 3 years of follow-up), mainly due to lost to follow-up (54% and 10% for missing variables of patients still in follow-up). Baseline characteristics between patients with data on DFR at 3 years did not remarkably differ, which reassured us that our results were not biased by differences between patients that were and were not lost to follow-up. Finally, our study was executed in a treat-to-target setting, in which treatment was intensified and tapered according to a fixed medication protocol. Although a treat-to target management approach is recommended for RA, this protocolized treatment regimen might not be completely generalizable to a real-life setting, in which treatment decisions are also based on the perspective of the treating rheumatologist and patient.

Conclusion

The presence of IgA ACPA and IgA RF almost completely overlaps with the presence of the commonly measured isotypes IgG ACPA and IgM RF. In addition, both presence of IgA ACPA and IgA RF seems to have no additional value over concomitant IgG ACPA and IgM RF presence for the outcomes of 'quick-attained and persistent' remission, achievement of DFR and biological use in an early arthritis population with a treat-to-target approach. The small numerical difference for IgA positive patients for these outcomes in the IgG ACPA positive group could be a reflection of a stronger humoral autoimmunity causing a slightly worse disease course in these patients. To conclude, there seems to be no rationale for measuring IgA ACPA and IgA RF in daily clinical practice.

Abbreviations RA: Rheumatoid arthritis; ACPA: Anti-citrullinated protein antibody; RF: Rheumatoid factor; IA: Inflammatory arthritis; DFR: DMARD-free remission; tREACH trial: Treatment in the Rotterdam Early Arthritis Cohort trial; MTX: Methotrexate; SASP: Sulfasalazine; HCQ: Hydroxychloroquine; GC: Glucocorticoid; DAS: Disease activity score; FEIA: Fluorescence enzyme immunoassay

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12026-024-09500-w.

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Author contribution JH, MWJS, AHMvdHvM and PHPdJ contributed to the conception and study design. JWH analysed and interpreted the

data. JHSAMK performed and MWJS supervised the autoantibody measurements. JWH wrote the first version of the manuscript, and MWJS, AL, AHMvdHVM and PHPdJ revised it critically. PHPdJ and AHMvdHvM supervised the study. All authors read and approved the manuscript.

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Data availability The data used in this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The tREACH was approved by the local medical ethics committee of the Erasmus Medical Centre, Rotterdam, The Netherlands (MEC-2006–252). All patients gave written informed consent before inclusion.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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