Baseline serum immunoglobulin levels in patients with rheumatoid arthritis: relationships with clinical parameters and with B-cell dynamics following rituximab

I. de la Torre[1,2], M.J. Leandro[1], J.C.W. Edwards[1], G. Cambridge[1]

[1]Centre for Rheumatology, University College of London, London, United Kingdom;
[2]Rheumatology Division, Hospital Gregorio Maranon, Madrid, Spain.

Abstract

Introduction

To investigate whether levels of serum immunoglobulins (sIgs) at baseline were associated with clinical parameters or B-cell dynamics following rituximab (RTX) in patients with rheumatoid arthritis (RA).

Methods

Baseline Ig levels, C-reactive protein (CRP), DAS28 and CD19+ve B-cell count (baseline, 1, 3 and 5 months) in 112 patients with RA after 1 cycle of RTX were included. All showed adequate B-cell depletion (<5 CD19+B cells/µl) after 1 month. Normal sIg ranges were for IgA (0.7-4.0 g/L), IgG (7.0-16.0 g/L), and IgM (0.4-2.3 g/L).

Results

Baseline IgA levels were raised in 29 patients, IgG in 18 and IgM in 11. CRP levels were significantly higher in patients with raised IgA and IgG compared to patients with normal levels (p=0.0002; p=0.03). At nadir after RTX, median levels of all sIgs decreased significantly although 16 patients (55%) remained with raised IgA, 28% IgG (5/18) and 27% IgM (3/11). Patients with raised IgA had higher minimum levels reached of CRP and of DAS28 (p=0.002; p=05). After 5 months, a higher percentage of patients with raised baseline sIgA had repopulated and were found to have shorter clinical responses than those with sIgs within normal limits.

Conclusions

sIgA levels in RA patients remained raised in a higher proportion of patients than other sIg after RTX. Raised sIgA was associated with a less robust clinical response to RTX and with B-cell repopulation coincident with relapse. Expanded or more permissive microenvironments for long-lived IgA plasma cells may be related to the presence of disease more refractive to B-cell depletion therapy.

Key words
B cells, rituximab, rheumatoid arthritis, IgA

Inmaculada de la Torre, MD
Maria J. Leandro, MD
Jonathan C.W. Edwards, PhD
Geraldine Cambridge, MD

Please address correspondence to:
Dr Geraldine Cambridge,
Division of Rheumatology,
Room 416, Rayne Institute,
5 University St,
London WC1E 6JF, United Kingdom.
E-mail: g.cambridge@ucl.ac.uk

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Introduction

Circulating IgA class autoantibodies have been related to the onset of disease in patients with rheumatoid arthritis (RA) and their relative levels with increased disease severity and incidence of erosions (1, 2). In humans, IgA is produced in the greatest overall quantity, generally in the form of dimers in the mucosa; serum IgA is mainly monomeric and is primarily produced by bone marrow plasma cells (3, 4, 5). Following B-cell depletion therapy (BCDT) based on rituximab (RTX) in patients with RA, B-cell return mirrors ontogeny (6). Full maturation of B-cell populations and restoration of an adult B-cell repertoire may however take years and it is not known whether it is always adequately achieved. Levels of serum immunoglobulin (Ig) isotypes also vary in their response to RTX, perhaps reflecting the rate of attrition of short- and long-lived plasma cells. It is well described that IgG and IgM levels can be raised in patients with RA. These usually normalise in most patients after repopulation in the first cycle of RTX (7). In some cases however, repeated cycles of RTX lead to a significant lowering, especially of IgM (8). Recent data from clinical trials showed that after 5 cycles of BCDT, decreases in IgG levels varied, with from 3 to 6% of patients affected after each cycle started (8) although others have reported higher frequencies (7). In contrast, we found that serum IgA levels remained relatively stable and if elevated pre-RTX, did not normalise in all patients following RTX. Repeated cycles resulted in only <1% of patients with levels significantly decreased below the normal range (7, 8).

Serum IgG levels greater that 12.7g/L and seropositivity at baseline have been associated with EULAR response at 24 weeks after rituximab (9), but the significance of raised pre-RTX serum IgA levels and the relationship with clinical and biological parameters have not yet been explored. As part of an on-going prospective study to identify immunological parameters associated with mechanisms underlying the clinical response to B-cell targeted therapies, we investigated whether raised total serum IgA, IgG or IgM at baseline was associated with particular clinical features or B-cell dynamics after RTX.

Methods

Patients

One hundred and twelve patients who fulfilled the American College of Rheumatology (ACR) criteria for RA (10) were studied on the basis of pre-treatment (before 1st RTX cycle) total serum IgA, IgG and IgM levels measured by nephelometry. Patients were subsequently grouped related to baseline (pre-RTX) total Ig levels: Normal IgA (0.7–4.0 g/L), Raised baseline IgA (>4.0 g/L), Normal IgG (7.0–16.0 g/L), Raised baseline IgG (>16.0 g/L), Normal IgM (0.4–2.3 g/L) and Raised baseline IgM (>2.3 g/L). Cut-off levels were those used by the University College London Hospitals (UCLH) Pathology Services Laboratory.

The patients were all attending the Department of Rheumatology at UCLH. The mean age was 53 yrs (range 36–86) and the mean disease duration was 21 yrs (range 8–50). 8 patients were RhF negative. They were treated with BCDT using rituximab on the basis of clinical need (non-fixed retreatment based on clinical need at variable intervals not shorter than six months, as previously described) (7). None of the patients presented with either active or chronic liver or enteropathic conditions but one was affected with celiac disease. Only patients who had achieved adequate B-cell depletion at 1 month following rituximab (as defined below; Blood sampling and CD19 counts) were included. The study was approved by the UCLH Ethics Committee and all patients gave informed consent before entering the study.

Baseline and minimum levels for serum C-reactive protein (CRP) and DAS28, time to repopulation and time to clinical relapse were collected retrospectively. Clinical response was defined as using the European League Against Rheumatism (EULAR)/Disease Activity Score for 28 joints (DAS28) criteria (11). Clinical relapse after BCDT was based on (i) any return of symptoms of RA plus a (ii) rise in CRP following an original fall of at least 50% in CRP during the previous course of RTX (7).

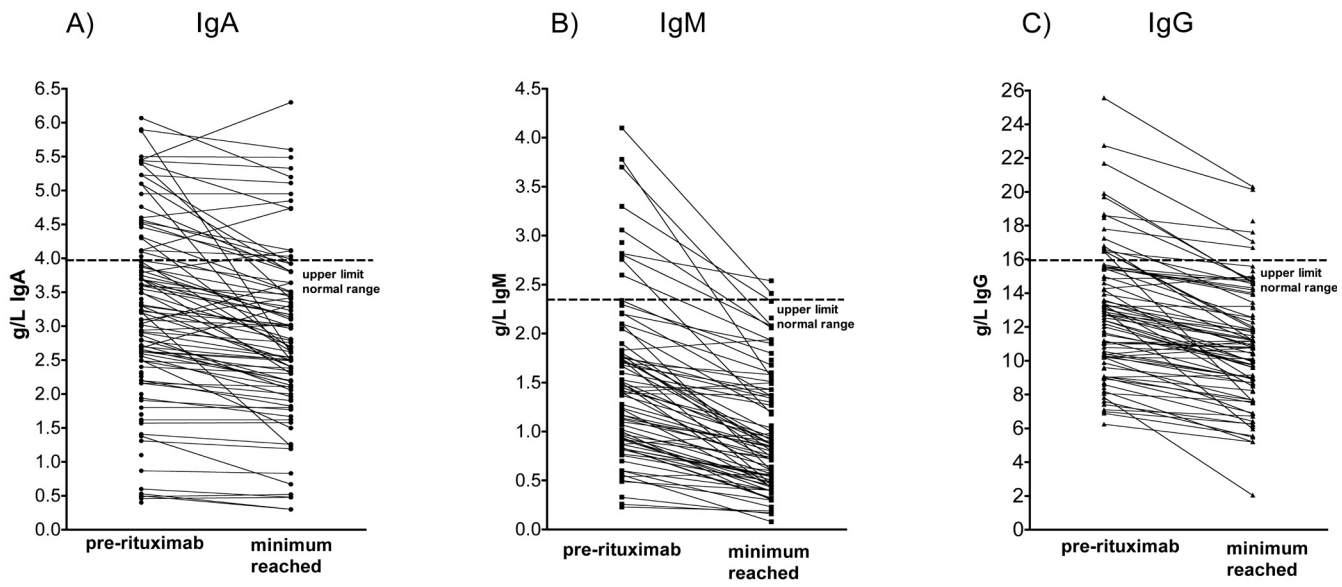


Fig. 1. Pre-treatment and minimum values reached for serum IgA (Fig. 1A), IgM (Fig. 1B) and IgG (Fig. 1C) within the first cycle of BCDT in 112 patients with rheumatoid arthritis. Exact significance levels were calculated using Wilcoxon non-parametric analysis for paired data.

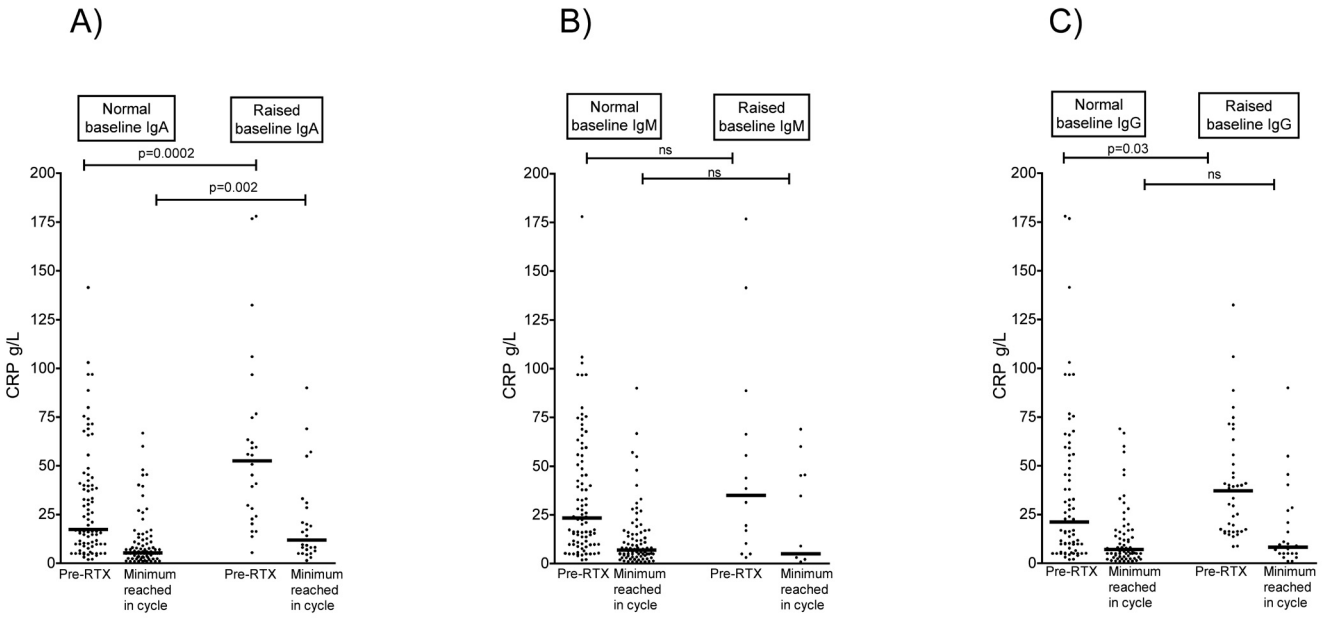


Fig. 2. (**A-C**). CRP levels in RA patients pre-RTX and when minimum value within the cycle of treatment was reached in patients grouped for baseline levels of IgA (A), IgM (**B**) and IgG (**C**). Wilcoxon Rank sum analysis was used to compare paired samples within each isotype pre-RTX and at minimum value reached. Asterisks denote *p*-values as follows***$p<0.0001$, **$p<0.005$, *$p<0.01$. CRP levels in patients with either normal or raised baseline sIg pre-RTX and the minimum values reached within the cycle of treatment are indicated for each Ig isotype. Results were compared using Mann-Whitney U-test and are indicated on the graphs. Lines in each graph denote median levels.

Blood sampling and CD19 counts

For all patients, blood samples were obtained at baseline, at 1 month and every 2 to 3 months thereafter at the outpatient clinic at UCLH and CD19+ B cell absolute numbers determined. The normal range for CD19+ B cells used by the UCLH Pathology Services laboratory was 0.03-0.40x10^9/litre with a minimum limit detection ≥5x10^6/L. Adequate depletion of B cells in the peripheral blood was deemed to have occurred when CD19+ B cells were <5x10^6/L (<5 CD19+ B cells/μl). B-cell return (B-cell repopulation) was defined as when the CD19+ B-cell count was again ≥5x10^6/L (≥5 CD19 cells/μl) (6, 7). IgA and IgM class rheumatoid Factor (RhF) levels and IgA, IgM and IgG anti-cyclic-citrullinated peptides (CCP(subclasses and B-cell activating factor of the TNF family (BAFF) were measured using ELISA as previously described (12, 13).

Statistical analyses

Non parametric tests were performed for independent and paired parameters (Mann-Whitney U and Wilcoxon test) and Fisher's exact test for comparing

patient groups. Multivariate analysis was performed using SPS For Windows.

Results

Serum Ig levels pre-RTX and at lowest level reached

Serum Ig levels in 112 RA patients before their initial cycle of B-cell depletion therapy, and the lowest achieved within that cycle, are shown for serum IgA, IgM and IgG, respectively in Figure 1 (A-C). IgA levels were above the upper limit of normal range in more than 25% (29/112) of the patients before treatment. IgG and IgM levels were raised in 18 and 11 patients respectively. Of interest, in the 29 patients with raised baseline IgA, only 6 also had raised IgG (>16g/L) and only 1 of the patients with raised baseline IgA patients also had raised IgM (>2.3g/L). None of the 112 patients had raised levels of all 3 serum Ig isotypes simultaneously at baseline. Although significant decreases of all 3 isotypes was found from baseline to nadir (indicated in Fig. 1; Wilcoxon non-parametric analysis for paired data) decreases in IgA only reached the 5% significance level with 55% (16/29) patients remaining with raised IgA levels compared with 28% (5/18) with IgG and 27% (3/11) with raised IgM. In addition, as we have previously described (7), the majority of patients with raised IgA pre-RTX did not normalise prior to their next cycle of treatment (data not shown).

Clinical response to RTX in relation to serum Ig levels

In order to explore serological and clinical characteristics of patients with baseline Ig levels within, compared with those with levels above the normal range, pre-treatment and minimum levels of CRP and DAS28 achieved within the first treatment cycle were determined and are plotted for each Ig isotype (Figs. 2-3). Median CRP levels at baseline were higher in those patients with raised baseline IgA and IgG (p=0.0002 and p=0.03 respectively, Mann-Whitney U-test). CRP levels decreased significantly after RTX irrespective of whether baseline sIg levels were within or above normal ranges (Wilcoxon paired analysis; p<0.0001). Patients with raised baseline IgA, however remained with a significantly higher minimum CRP after RTX (p=0.002; Fig. 2A) whereas minimum CRP levels were similar in patients with normal and raised IgM and IgG; (Fig. 2B-2C). DAS28 scores at baseline and minimum reached are shown for all Ig isotypes in Figure 3. Patients with raised pre-RTX IgM levels had a higher starting DAS28 score (Fig. 3B; p<0.05; Mann-Whitney U-test), with patients with raised baseline IgA approaching significance (Fig. 3A; p=0.08). Median levels of DAS28 decreased significantly in all groups after RTX (p<0.01) but the decrease in DAS28 from baseline in patients within the high IgA group was relatively less (p<0.01) than the decrease from baseline DAS28 in patients in the Normal IgA group (p<0.0001). Patients with raised levels of IgA pre-RTX also had less of a drease in DAS28 compared with those patients with serum IgA within normal limits (p=0.05; Fig. 3A).

Pattern of B-cell return in relation to pre-RTX serum Ig levels

In Table I the number of patients who would be considered in the clinic to have

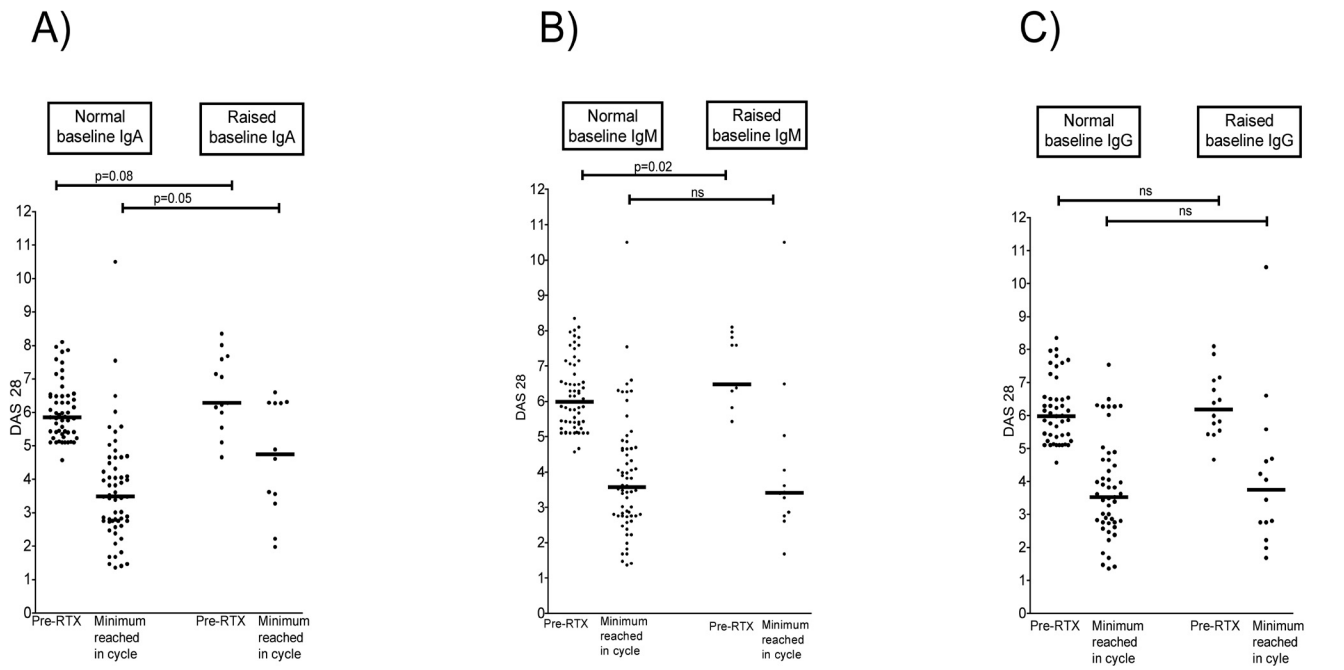


Fig. 3. (A-C). DAS28 levels in RA patients pre-RTX and when the minimum value within the cycle of treatment was reached for patients grouped for baseline levels of IgA (**A**), IgM (**B**) and IgG (**C**). Wilcoxon non-parametric analysis was used to compare paired samples within each isotype pre-RTX and at minimum value reached. Asterisks denote p-values as follows***p<0.0001, **p<0.005, * p<0.01. DAS28 in patients with either normal or raised baseline sIg pre-RTX and the minimum values reached within the cycle of treatment are indicated for each Ig isotype. Results were compared using Mann-Whitney U-test and are indicated on the graphs. The lines in each graph denote median levels.

Table I. B-cell return following RTX: relationship with baseline IgA and IgG immunoglobulin levels.

Baseline Ig Group	Number and % patients with CD19+ cells >5/µl 3 months after RTX	Number and % patients with CD19+ cells >5/µl 5 months after RTX
High IgA	9/26 (34.6%)	15/23 (65.2%)*
Normal IgA	6/44 (13.6%)	13/49 (26.5%)
High IgG	4/20 (20.0%)	10/17 (58.8%)
Normal IgG	8/40 (20.0%)	15/44 (34.1%)

*p=0.04 compared with Normal IgA Group (Chi-Square analysis).

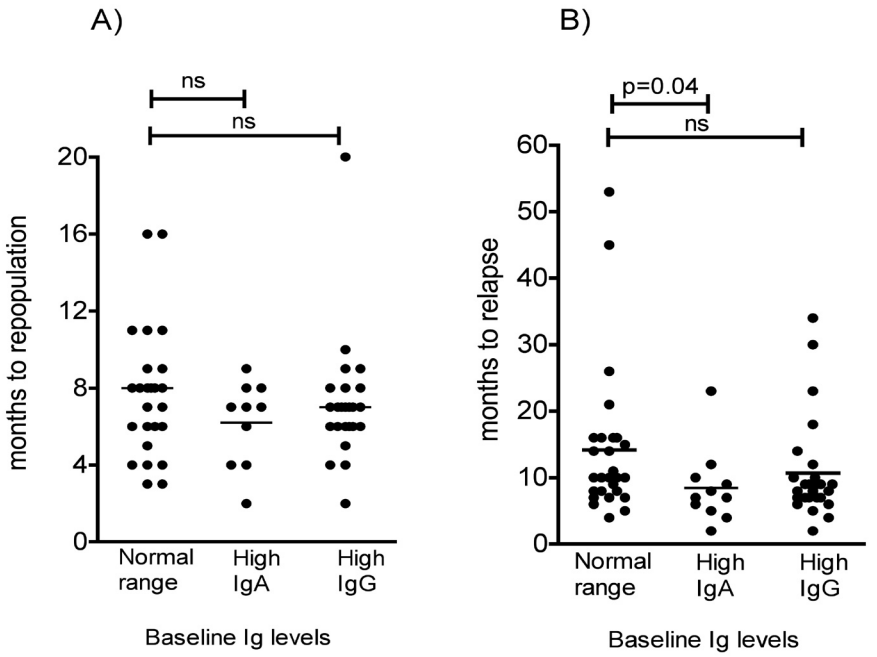


Fig. 4. Time in months to B cell return (A) and to clinical relapse (B) (both as defined in Methods). Patients were treated with RTX at Time 0. Patient groups consisted of those with both IgA and IgG within normal ranges compared with those with either elevated baseline serum IgA or IgG. Median levels were compared using Mann Whitney U test.

re-populated (B-cell counts >5 CD19+ per µl) at 3 and 5 months post-RTX are shown. The proportion of patients re-populated at both these time points appears to be greatest in those with raised pre-RTX IgA levels although this only becomes statistically significant after 5 months. There was also a tendency for a higher percentage of patients with raised baseline IgG to have repopulated at 5 months compared with those starting with IgG levels within the normal range, but this was not significant (Table I). Patients with raised baseline IgA were also found to have significantly higher B-cell counts 5 months after RTX than their counterparts with IgA within normal limits (p=0.04; data not shown. Supplementary Data 1).

Time to repopulation and to relapse in patients with different starting levels of serum Ig isotypes

In our cohort of patients at UCL, the detection of significant numbers of B cells (>5 CD19+ cells/µl) in the peripheral blood after RTX therapy heralds clinical relapse in approximately 60% of RA patients. Both groups of patients with raised baseline levels of IgG and IgA tended to have a greater tendency than predicted to undergo clinical relapse when significant numbers of B cells became detectable in peripheral blood (76% and 88% respectively; data not shown). The time in months to repopulation and to relapse was therefore compared between the different groups of patients (Fig. 4). Due to the limited data available for this analysis, patients with serum IgG and IgA within the normal range were pooled. There was no difference in the median months to repopulation between those patients with raised baseline IgA or IgG and patients having normal baseline Igs (Fig. 4A). There was however a significantly shorter time to relapse in the raised baseline IgA group (p=0.04) (Fig. 4B), with only 1 patient in this group achieving a EULAR/DAS28 response for >12 months

Possible contribution of confounding factors

The most striking finding in this study was that patients with raised pre-treatment serum IgG and IgA were both more likely to have significantly higher CRP levels, but only those with raised baseline IgA apparently responded differently from patients with IgA within the normal range. We therefore performed statistical tests to determine whether there were any confounding factors contributing to these findings. Multiple linear regression analysis of age and concomitant DMARD were not found to influence the results (data not shown). Serum autoantibody and BAFF levels did not differ significantly between patients with raised baseline sIgs and those within the normal range for any of the 3 isotypes (Supplementary Data 2).

Discussion

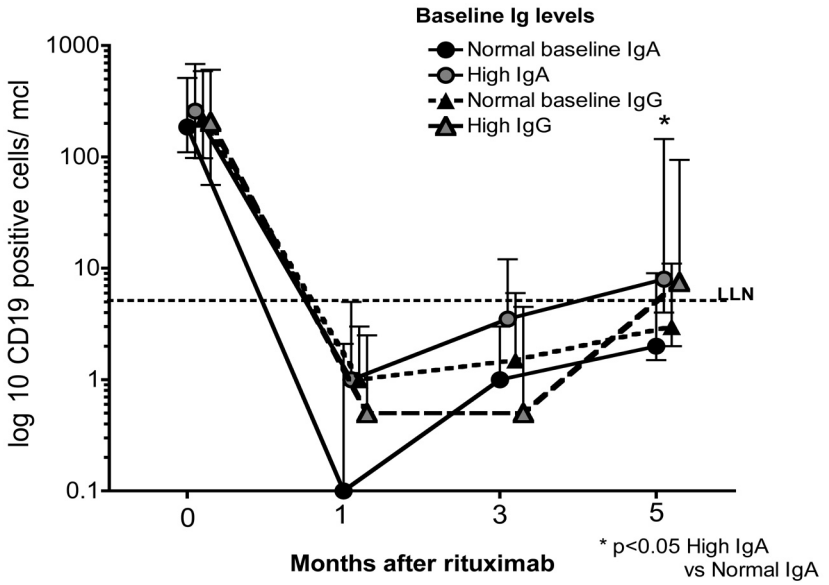
In RA patients undergoing B-cell depletion therapy based on RTX, levels of serum total IgA do not decrease to the same extent as IgG or IgM (7, 8). In the current series, a higher proportion of patients with raised baseline serum IgA, compared to those with IgA or IgG levels within the normal range, had repopulated in the peripheral blood at 5 months after RTX. This was not due to a global increase in serum Ig levels as only 21% of patients with raised IgA at baseline also had raised serum IgG and only 3%, raised IgM. Patients with raised baseline IgA also tended to relapse closer to the time of B-cell return. Importantly, patients with a high proportion of longer clinical responses were largely confined to the patients

with serum IgG and IgA within the normal range (Fig. 4B).

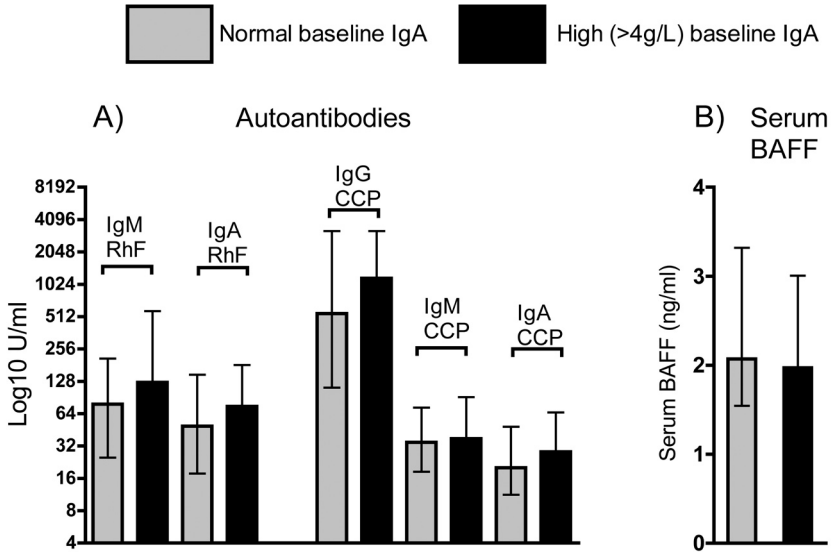
Patients with raised baseline IgA also showed a higher median CRP and a tendency for higher DAS28 at baseline and did not show as marked a decrease in median levels of both CRP and DAS28 at nadir following RTX. The questions raised by these findings are therefore: 1) why are raised levels of IgA associated with the acute phase response and a relatively more resistant phenotype of joint disease, and 2) how is this related to shorter clinical responses which were more closely associated with the return of B cells?

IgA antibodies are the most abundant immunoglobulin class, being secreted onto mucosal surfaces as dimers. Serum IgA is virtually exclusively monomeric. Studies of IgA expressing pre-plasma cells in normal individuals have shown that in peripheral blood, $CD27^{hi}CCR10+sIgA$ positive pre-plasma cells can be induced to secrete polymeric, not monomeric IgA and that most monomeric IgA must come from the bone marrow (4). Whether the raised baseline levels of serum IgA in our series reflect monomeric IgA production by bone marrow plasma cells or, on the other hand, polymeric IgA production by intestinal mucosal plasma cell activity, was not addressed but as polymeric IgA is rapidly cleared by the liver (14), it is more likely to be the monomeric form. None of the patients included had evidence of significant liver disease (data not shown). The finding of raised serum IgA levels in our cohort of RA patients may simply be a measure of an increased availability of survival niches in the bone marrow for IgA plasma cells. Plasma cells are also known to home non-specifically to sites of inflammation and therefore they may also reside in the joint, or possibly the lung in patients with RA. The correlation with CRP would support the possibility that serum IgA is behaving as an acute phase reactant, being associated therefore with more severe inflammation.

During the time when B cells are depleted, the presence of small numbers of circulating plasmablasts expressing IgA, many also with CCR10 and $alpha_4beta_7$ integrin, has been described.



Supplementary Data 1. Time course showing mean and 95% confidence intervals for absolute numbers of CD19+ B cells following B cell depletion therapy with RTX. Dotted line indicates the lower limit of the normal range (LLN) for B cell depletion (5 CD19+ cells/μl) used in the clinic. Patients were divided on the basis of having normal or raised levels of serum IgA or IgG at baseline, as indicated. Analysis of median values for each patient group at all the time points showed that there were significantly greater numbegrs of CD19+ B cells present in peripheral blood from patients who started with raised IgA than in patients who started with normal levels of IgA (Mann-Whitney U-test, $p<0.05$).



Supplementary Data 2. **A**) Shows median and interquartile ranges for IgM and IgA. Rheumatoid factors and for IgG, IgM and IgA class anti-CCP antibodies in patients with RA grouped on the basis of Normal or High serum IgA levels. **B**) Similarly shows serum BAFF levels for the two groups of patients. There were no significant differences between any of the pairs of values of autoantibodies or BAFF (Mann-Whitney Rank sum analysis $p>0.05$).

It is likely, as has been suggested by Mei *et al*. (15), that these represent a 'steady state' recirculation of IgA mucosal pre-plasma cells generated as a consequence of on-going mucosal IgA antibody production which are homing to other mucosal sites and are committed to polymeric IgA production. The relative resistance of monomeric IgA to RTX therefore suggests that the IgA-producing plasma cells in the bone marrow and/or inflammatory sites are a very stable population or that their parent B cells are not depleted by RTX.

The association of raised serum IgA with B-cell kinetics is not so clear, but perhaps suggests that changes in the bone marrow, secondary to a disease associated pro-inflammatory environment, may be influencing B-cell regeneration after rituximab. As well as having different functional properties, the main isotypes of serum Ig are regulated differently. B-cell and plasma-cell development and maintenance are largely dependant on concerted expression of B-cell activating factor (BAFF)-binding receptors. Studies of patients with hypogammaglobulinaemia related to mutations in BAFF-receptors have shown that IgG and IgM production were at least partially dependent of BAFF signaling through BAFF-R (BR3) whereas class-switch to IgA production seems to rely on signaling through TACI (transmembrane activator and calcium-modulator and cytophilin ligand interactor) mainly by binding APRIL, not BAFF (16, 17). The molecular mechanisms for B-cell or plasma-cell survival responsible for raised IgA are not clear. Disturbances in TACI signaling and treatment with TACI-Ig have been related to decreased IgA production (18). We have previously reported that changes in the relative expression of receptors for BAFF (BAFF-R,TACI and BCMA) (19, 20) on B cells from RA patients were related to relapse. Due to the importance of co-ordinated BBR expression for B-cell survival and differentiation to plasma cells, previously undetected or treatment-induced (RTX) changes in BBR expression and signaling may also affect serum Ig homeostasis. Whether raised serum IgA reflects an increase in class-switch to IgA or to pro-survival factors for plasma cells operating in the bone marrow remains to be determined.

The aim of the present study was to explore our initial observation that serum IgA levels behaved differently from IgG and IgM following rituximab and secondly, the unusually high proportion of patients with RA having raised serum IgA levels. We found that the subgroup of patients with RA presenting with raised baseline total IgA levels showed a tendency for more robust B cell return, higher minimum levels reached of CRP and DAS28 and also were found to relapse closer to the time of B-cell return. Based on these findings, this group of patients may particularly benefit from early second retreatment in order to prevent relapse and achieve a better and more sustained control of the disease.

Key messages

- Raised serum IgA is associated with higher starting CRP and less robust DAS28 response
- The proportion of patients with significant B-cell repopulation at 5 months after rituximab is higher in these patients
- Patients starting with raised baseline IgA also tend to have shorter clinical responses to rituximab

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