Editorial

What Can We Learn from Treatment-Induced Changes in Rheumatoid Factor and Anti-Citrullinated Peptide Antibodies?

Basic and clinical research initiatives on the 2 major autoantibody systems in rheumatoid arthritis (RA), rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), have moved in parallel in recent years[1-3]. Indeed, recent works have disclosed some of the mechanisms underlying the genesis, maintenance, and role of the humoral autoimmune response in RA, identifying defective B cell tolerance checkpoints[4] and dissecting the interactions among environment, genes, and adaptive immunity[3]. On the other hand, monitoring the autoimmune response in RA through its most accessible marker, i.e., serum autoantibodies, has gained growing interest as RF and ACPA are recognized as powerful predictive, diagnostic, and prognostic tools in RA.

Several studies in recent years have focused on changes in RF and ACPA levels during different treatment strategies, especially with biological agents such as tumor necrosis factor-α (TNF-α) inhibitors, summarized in Table 1[5], and B cell targeted therapies[6]. These studies are welcome for a number of reasons. First, the identification of different pretreatment values and/or different rates of decline of RF and ACPA might offer accessible biomarkers of clinical response. Second, treatment-related changes of serum autoantibodies might provide insights into the specific immunoregulatory activity of a single drug or class of drugs. Third, monitoring the serum autoimmune response in RA might shed new light on mechanisms underlying the generation and maintenance of autoreactive B cells. Last, assuming that autoantibodies play a pathogenetic role in RA, treatment-induced seroconversion could be regarded as one of the goals for true remission or cure.

The article by Bos and colleagues[7] in this issue of *The Journal* provides a significant step forward in understanding the serum autoimmune response after effective treatment in RA: the authors analyze a large cohort of patients homogeneously treated with adalimumab. The results emerging from their study are: (1) decrease from baseline values is much greater for IgM RF with respect to ACPA (31% vs 8%); (2) seroconversion (from positive to negative) is unusual for ACPA, while 17% of patients become negative for IgM RF; and (3) decreased antibody levels are associated with clinical response for both IgM RF and ACPA, and with decreased acute-phase reactants for IgM RF.

A drop in IgM RF levels has been nearly unanimously reported with TNF-α inhibitors (Table 1) as well as with other biological and conventional disease modifying antirheumatic drugs (DMARD)[6,8,9]. Such decrease was shown to be stable over time[10], and a more conspicuous decline was associated with good clinical response[11]. IgA and IgG RF isotypes are also strongly reduced by conventional DMARD and TNF-α inhibitors, although this decrease does not appear to be related to clinical response[8,11]. Changes in ACPA have been less consistent (Table 1), possibly due to different assays for ACPA measurement, different disease duration, different study periods, and different criteria of analysis (inclusion of all patients vs positive patients only). Data provided by Bos and colleagues[7] indicate that, although a significant drop of IgG ACPA can be observed in patients achieving clinical response, ACPA levels are much less affected than RF by TNF-α inhibitors, as also reported with rituximab[6] and conventional DMARD[9]. It remains to be determined whether the reduction in ACPA levels is as stable as that found for IgM RF[10].

A direct application of these results in clinical practice appears at present to be just fascinating. Indeed, no data support a better performance of autoantibody measurement with respect to acute-phase reactants and clinical assessment in monitoring response to therapy. Until the temporal relationship is specifically dissected, it remains undetermined whether IgM RF levels are a consequence of inflammation (thus being a redundant marker) rather than a cause. Further, it is still unclear whether pretreatment levels of different autoantibodies and/or isotypes may be able to predict

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Table 1. Characteristics of longitudinal studies on RF and ACPA levels during RA treatment with TNF-α inhibitors.

Study	Treatment	Patients, n	Followup, weeks	RF IgM	RF IgG	RF IgA	ACPA (IgG)
Bobbio-Pallavicini[10]	Infliximab/MTX	30	30; 78	50% decrease (sustained at 78 wks)	—	—	Small decrease (not sustained at 78 wks)
Nissinen[19]	Infliximab/DMARD	25	2	Decrease	—	—	No effect
Alessandri[20]	Infliximab/DMARD	43	24	20% decrease (responders)	—	—	15% decrease (responders)
Caramaschi[21]	Infliximab/MTX	27	22	50% decrease	—	—	No effect
De Rycke[22]	Infliximab/MTX	62	30	50% decrease	—	—	No effect
Yazdani-Biuki[23]	Etanercept/DMARD	12	36	No effect	~40% increase	~35% increase	No effect
Braun-Moscovici[24]	Infliximab/DMARD	30	14	No effect	—	—	Decrease (responders)
Chen[25]	Etanercept/DMARD	90	12	35% decrease (responders)	—	—	30% decrease (responders)
Atzeni[26]	Adalimumab/MTX	57	48	40% decrease (responders)	—	—	30% decrease (responders)
Ahmed[27]	Infliximab/DMARD	33	30; 54	Decrease (sustained at 54 wks)	No effect	Decrease (not sustained at 54 wks)	Decrease (not sustained at 54 wks)
Bobbio-Pallavicini[11]	Infliximab/MTX, etanercept/MTX, adalimumab/DMARD	132	54	25% decrease (responders)	20% decrease (responders and nonresponders)	10% decrease (responders and nonresponders)	No effect
Vis[28]	Infliximab/MTX	62	46	65% decrease	—	—	25% decrease

ACPA: anti-citrullinated peptide antibodies; DMARD: disease modifying antirheumatic drugs; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; TNF-α: tumor necrosis factor-α; TLR: Toll-like receptors.

different response rates to different therapies[5]. Additional studies are warranted on this topic.

Translating these results into basic research is even more speculative. Indeed, the mechanisms that underlie the ability of TNF-α inhibitors to decrease RA-specific autoantibodies are far from fully elucidated, although several pathways have recently been explored[12]. These include restoration of the regulatory T cell pool and function, inhibition of dendritic cell maturation, inhibition of interleukin 6 and B cell activating factor synthesis and Toll-like receptor (TLR) expression, and, more recently, direct interference with the B cell compartment through disruption of germinal centers[13]. It is likely that such mechanisms, at least in part, are not class-specific but are shared by most of the immunomodulatory drugs in RA, as conventional DMARD and B cell targeted therapies have shown similar patterns of reduction of RF and ACPA[6,8,9].

More intriguingly, the marked qualitative and quantitative differential responses of RF and ACPA during antirheumatic treatment raises the important question of whether and how the 2 autoantibody systems are differently regulated. Although little is known about IgM ACPA fluctuations, such different behavior is not fully attributable to a different clearance between the IgG isotype of ACPA and the IgM isotype of the RF, since marked reduction of all RF isotypes has been described after both anti-TNF-α[11] and rituximab treatment[6]. Again, it is likely that several mechanisms account for the diversity of the RF and the ACPA systems. Although only speculative, these might include: (1) different roles of innate and adaptive immunity, as suggested by the ability of TLR to activate RF+ B cells[14] and, in contrast, the strong association of ACPA with major histocompatibility complex-class II susceptibility loci and the requirement of T cell help[3]; (2) a different contribution of various antibody-secreting cells, such as plasmablasts, short-lived and long-lived plasma cells[15], characterized by different lifespans, different environmental niches, and different responses to therapies; (3) different sites of production, which include spleen, bone marrow, lymph nodes, and the synovial tissue itself, as well as other ectopic lymphoid sites[16-18], possibly characterized by different accessibility and different ability to host B cell responses and support plasma cell survival.

We cannot predict whether monitoring RF and ACPA levels during therapies will ever enter routine clinical practice. However, we encourage further research as the understanding of treatment-induced changes of autoantibody levels provides a framework for dissecting the pathophysiological bases of the B cell autoimmune response in RA.

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