Is ACPA positivity the main driver for rheumatoid arthritis treatment?
Pros and cons

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Abstract
Rheumatoid Arthritis (RA) is an autoimmune chronic disease that is characterized by the positivity of various antibodies, the most specific being autoantibodies against citrullinated antigens (ACPA). Despite ACPA are not arthritogenic by themselves, ACPA positive individuals have high risk of RA development and ACPA positivity is associated with severe erosive phenotype and higher mortality rate compared to seronegative RA. Moreover, ACPA status is associated with favorable response to biologics targeting pathways involving autoantibody producing cells as B lymphocytes. In the current review we have discussed the pros and cons on the available scientific evidences, regarding the diagnostic, prognostic and management implications of ACPAs in RA.

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1. Introduction

Rheumatoid Arthritis (RA) is a chronic multifactorial systemic autoimmune disease leading to inflammation of synovial joints and erosions of bone resulting in pain, joint destruction and disability [1].

It is also a systemic inflammatory disease that can lead to several comorbidities if not adequately controlled through an early diagnosis and an appropriate therapeutic approach.

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RA is characterized by the positivity of various antibodies, the most specific being autoantibodies against citrullinated antigens that derive from arginine by post-translational modification induced by peptidyl arginine deiminases (PADs) activity [2]. These antibodies were first identified in 1964 as antibodies against perinuclear granules in the superficial cells of the human buccal mucosa epithelium (anti perinuclear antibodies-APF) [3]. In 1995 it was shown that flaggrin is the common antigen targeted by both APF and AKA [4]. This led to the development of ELISA tests: CCP-1 using flaggrin-derived cyclic peptide [5] and currently CCP-2 which utilizes a mixture of cyclic citrullinated peptides and made commercially available in 2002. Several other ACPA assays were also developed (CCP-3, MCV) [6].

The purpose of the current review is to discuss the current pros and cons on the scientific evidences available, regarding the diagnostic, prognostic and management implications of ACPAs in RA.

2. ACPA as the main pathogenic driver in RA

2.1. Pros

ACPA are present in nearly two thirds of RA patients and are more specific than rheumatoid factor (RF) for RA [5,7–9]. In many cases, the diagnosis of RA is made clinically and is often delayed by an initial period of non-specific symptoms. However it is generally accepted that there is a window of opportunity for an early aggressive management of RA and that the disease management delay may result in increase of joint damage and disability [10].

In this context, Brink M et al. analyzed a large cohort of individuals at risk of developing RA showing that the development of an immune response toward citrullinated peptides is initially restricted but expands with time to induce a more specific response, with autoantibodies levels increasing during the predating time period closer to the onset of clinical symptoms [11]. Moreover, Sokolove J and coworkers observed a time-dependent expansion of ACPA specificity with an increase of ACPA subtypes suggesting an accumulation of multiple autoantibody specificities reflecting the process of epitope spreading [12]. In addition, years before RA onset, antibodies positivity is associated with inflammatory cytokines deregulation [13,14], (including TNF-α, IL-6, IL-12p70, and IFN-γ) suggesting that the autoimmune processes leading to clinical manifestation of arthritis is tightly related to the pro-inflammatory status. Therefore, ACPA’s role in the preclinical phase of RA seems not to be limited only to their high specificity for RA but even by their well-established association with a severe, erosive phenotype [15–18]. Moreover, a qualitative change in the ACPA response before disease onset was found as the Fc fragment glycosylation enhancing the inflammatory activity of IgG [19]. In particular, Rombouts et al. found a decrease of galactosylation and an increase of core fucosylation of serum ACPA-IgG, before the onset of RA [20]. Despite autoantibodies positivity in this early period, ACPA do not cause apparent pathology, since individuals at risk of RA development (ACPA and/or RF positive) do not show evidence of histologically proven synovitis in the preclinical phase, in terms of CD3 +, CD22 +, CD55 +, CD68 +, CD138 + cells [21]. However ACPA positivity fosters a wide range of systemic and local inflammatory processes [22] as enhancement of osteoclastogenesis, osteoclasts differentiation and bone resorption respectively [23]. In particular, a rapid radiographic progression was shown to be predicted by high ACPA titers in the ESPOIR cohort, and a reduction of systemic bone mineral density in RA patients at disease onset mainly in ACPA/RF seropositive patients [24,25]. In this context, Krishnamurty et al. found that ACPA, binding to osteoclast precursors, induce the expression and release of TNF-α together with an increase of IL-8 able to promote osteoclastogenesis in a dose-dependent manner [26]. These findings provide the biological basis for the detection of erosive damage in asymptomatic individuals at risk of developing RA before any clinical manifestation [27].

ACPA positive individuals showed changes in periarticular bone as thinning and fenestration of the cortical bone as well as milder changes in the trabecular bone [27]. These findings challenged the concept that bone damage in RA is exclusively led by inflammation. Moreover, the observation that the first bone change in at risk individuals is the cortical fenestration providing a direct anatomical connection between the bone marrow and the joint space is interesting since it is still unknown where ACPA producing plasmacells are firstly located. In fact, despite it is known that citrullination of proteins may occur at anatomical sites far from the joint, as lung epithelium [23] and gingival mucoa [28], it is still unknown where and how the loss of immunological tolerance takes place and where the ACPA production by autoreactive plasmacells firstly occurs [29].

The ability to identify and observe the break of immunological tolerance at the earliest stages of disease could provide significant insights into the pathogenesis of RA and could be used to guide initiation of disease modifying therapy at the earliest phases of the disease [30].

2.2. Cons

In 1957 Witebsky defined the criteria for the definition of an autoantibody as pathogenic based on Koch’s postulates of infectious agents’ pathogenicity [31]. These postulates have been revisited in 1993 by Rose and Bona [32] who stated that in order to be pathogenic an antibody has to fulfill the following three criteria:

1. The autoantibodies are detectable in all cases of the disease.
2. The disease can be reproduced experimentally by immunization with the antigen.
3. The disease is transferable by the relevant antibodies.

Among the three criteria, the first is that the autoantibody should be specific and sensitive to the disease. Data from a study of 12,590 twins from the National Swedish Twin Registry demonstrated that the Positive Predictive Value (PPV) of ACPA was only 29.4% and 48% for low and high ACPA titer respectively [33]. Similar results were reported in a larger population cohort from the Netherlands where only 22.4% of ACPA positive people had RA and 0.8% of healthy individuals were ACPA positive [34]. Therefore, ACPA is not found only in RA patients. Moreover, the sensitivity of ACPA is approximately 70%, meaning that many RA patients do not have ACPA [35]. This is also evident by the ACREULAR RA classification criteria which do not require ACPA positivity for diagnosis [36]. Therefore, ACPA are not necessary nor sufficient for RA development.

Regarding the second requirement is that immunization with the antigen will induce a disease similar to RA, many labs tried to induce the disease with the presumed self-antigen with no success. Immunization of rats with citrullinated fibrinogen induced anti-citrullinated fibrinogen antibodies but none of the immunized rats developed arthritis [37]. Only the addition of immunization with collagen led to the development of arthritis, indicating that citrullinated proteins may have some synergistic effect on the classic collagen-induced arthritis model, perhaps through generation of ACPA immune complexes and induction of clinical inflammation [38].

The third postulate is that the disease is transferable by the relevant antibodies. There are very few examples of induction of the human disease by human antibodies. Harrington injected himself deliberately with serum from a patient with ITP and developed thrombocytopenia. In addition, transplacental maternal to fetus transfer of neonatal Myasthenia Gravis, Graves’ disease, fetal heart block and fetal ITP have also been described [32]. We are not aware of any report of transplacental transfer of RA or development of arthritis after a blood donation from a seropositive RA patient. The most common way of fulfilling this criterion is the induction of disease in animals by passive transfer of autoantibodies. The injection of a panel of monoclonal anti-citrullinated fibrinogen antibodies into mice did not induce arthritis. Again, only
upon the addition of anti-collagen antibodies did arthritis develop [39]. Therefore, the Witebsky postulates for defining antibodies as pathogenic have not been fulfilled regarding the ACPA antibodies.

3. ACPA as the main diagnostic marker of RA

3.1. Pros

ACPA positivity is more specific than IgM-RF, IgG-RF or IgA-RF positivity for RA and is more specific than IgM-RF for early RA, with similar sensitivity (sensitivity of 67% and specificity of 95%) [40], despite anti-CCP2 test has a low sensitivity to be used as a screening test. However, in daily practice, a positive test is highly specific for RA and anti-CCP2 appears to be highly predictive of the future development of RA in both normal individuals and patients with undifferentiated arthritis [41,42].

Therefore, these tests appear to provide the best predictive assay to foresee which patients with recent onset of clinical synovitis would develop RA.

In clinical practice, to maximize sensitivity, most rheumatologists recommend measuring ACPA together with RF since ACPA have moderate sensitivity, especially for early RA [43]. The simultaneous evaluation of ACPA and RF provides a tradeoff between overall sensitivity and specificity. If the clinician wants to maximize sensitivity, then testing for both analytes is recommended, although this may lead to treat patients who are ACPA negative but RF positive and then risking to treat individuals with false-positive results who do not have RA [40]. On the contrary, ACPA alone seems to be a reasonable strategy when the probability of RA is relatively low, such as in patients who have monoarticular involvement only in primary care. However, in rheumatology outpatient setting, in which the probability of RA development is relatively high, measuring ACPA and/or IgM RF seems to be a reasonable strategy that avoids missing potentially treatable patients [44]. Moreover, it is interesting to note that a relatively extensive isotype usage in the ACPA response was detected in patients with recent-onset arthritis and that the presence of IgM ACPA in follow-up samples obtained from RA patients suggests an ongoing activation of new clones of ACPA–producing B cells, reflecting a continuous (re)activation of the RA-specific ACPA response during the course of ACPA–positive RA [45–48]. Therefore, in the diagnostic setting, testing for anti-CCP2 antibodies represents the gold standard of testing for ACPA with the highest sensitivity and specificity balance in the contest of all the known RA-related autoantibodies.

3.2. Cons

A meta-analysis of 87 studies examining the role of ACPA (37 studies) or Rheumatoid Factor (RF) (50 studies) in the diagnosis and prognosis of known or expected RA, showed that the specificity of ACPA was 95% and its sensitivity 67%, similar to that of RF (69%) [40]. Liao et al. showed that the addition of ACPA to the 1987 ACR criteria slightly improved the sensitivity of these criteria, from 51% to 55%, without improving its specificity [49]. These findings justified the addition of ACPA to the 2010 revised ACR classification criteria for RA. It should be noted that similar weight is given for the presence of ACPA and RF [36].

Established RA is easily diagnosed, whereas diagnosing the disease in its early stages is challenging. Unfortunately, at these stages of the disease, the value of ACPA is not too impressive. The sensitivity of ACPA in recent onset arthritis is 41–47% which is significantly lower than that found in the established disease (41–88%) [50]. The addition of ACPA to the ACR criteria failed to improve early RA diagnosis in a community-based very early arthritis cohort [51]. The Canadian Early Arthritis Cohort (CATCH) initiated a study to evaluate the effect of ACPA testing on the care of early RA patients. They looked at DAS28 after 3 months of treatment in groups with a known ACPA test in comparison to a group of RF negative patients without an ACPA test and found no difference in DAS28 and HAQ between the groups. They concluded that missing ACPA does not affect the short term outcome of early RA. This failure is likely due to its overlapping with the RF component [52].

In summary, ACPA is more specific to RA than RF however its addition to the ACR criteria improved the diagnostic sensitivity without improving early diagnosis.

4. ACPA as the main prognostic marker in RA

4.1. Pros

In RA daily management, it is clinically relevant the identification of prognostic marker for clinical outcome for a better selection of appropriate and cost-effective treatments. Both ACPA [53–55] and RF [56,57] have been shown to be associated with bone damage in RA.

In particular, in early RA the functional impairment is thought to be due mostly to the inflammatory burden expressed by disease activity [58] whereas, in long standing RA the disability is mostly linked to joint damage [59]. Both ACPA and RF are expression of the autoimmune response in RA patients and most of the studies have focused on the role of each autoantibody as individual whereas only few studies have investigated their interdependency for RA disease presentation [60,61]. Hecht et al. investigated the interdependency of ACPA and RF in RA mediated bone loss showing that the combination of both antibodies additively increases the burden of bone erosion mainly linked to ACPA since RF arose as important for bone erosions when ACPA are present [62]. Moreover, in a prospective study enrolling early RA patients followed for 10 years baseline radiographic score, ESR and ACPA positivity were the best predictive factors of the radiographic outcome [63].

In a prospective context, ACPA positivity was demonstrated to be associated with increased all-cause mortality in RA patients [64], mainly for cardiovascular (CV) disease [65]. Giles and colleagues showed a direct association between high titers of ACPA with lower myocardial mass and smaller left ventricular chamber volumes in RA patients without known CV disease [66]. Moreover, the same research group conducted a histopathological study showing that myocardial interstitium of RA shows higher degree of citrullination suggesting a possible link between autoimmunity and the known increase of myocardial dysfunction and heart failure in RA [67]. In addition, ACPA positivity was demonstrated to be associated with atherosclerosis even in the absence of RA symptoms [68] since citrullinated proteins and PAD presence were detected in atherosclerotic plaques [69]. Because of the availability of better treatment for RA, more patients experience remission in their disease course rising the question whether pharmacological treatment has to be continued lifelong or can be tapered or stopped. Therefore, once stable disease remission is achieved it is crucial the identification of possible biomarkers to be used in the selection of patients eligible to treatment tapering and discontinuation avoiding disease flare. The RETRO study was designed to improve decision making in RA patients in stable remission investigating predictors of relapse finding that ACPA positivity, but not RF, was an independent factor associated to disease flare together with treatment tapering or discontinuation [70].

4.2. Cons

Meyer et al. showed that serial determinations of ACPA may be a better predictor than RF (and baseline ACPA) to foresee radiographic joint destruction, as can be evaluated by erosions and joint space narrowing [71]. On the other hand, Bas et al. found that RF but not ACPA correlated with the Larsen score of joint damage and the development and the severity of erosions [72]. In patients participating in Rituximab and Golimumab clinical trials, the presence of RF rather than ACPA was associated with baseline disease activity as evaluated by SDAI, and similarly
RF but not ACPA was associated with a higher CDAI and DAS28 [73]. The correlation between RF or ACPA with disease activity measurements was also studied by Sokolove et al. [74]. Patients who were ACPA-positive and RF-negative had lower tender and swollen joint counts as well as DAS28 score than concordant seronegative patients and RF positive/ACPANegative patients, whereas RF-positive patients had significantly higher tender and swollen joint counts as well as DAS28. The highest levels of disease activity were found in patients who were seropositive for both RF and ACPA. When those researchers looked at the serum levels of inflammatory cytokines, such as TNF-α, IL-1 and IL-6, only the combination of RF and ACPA positivity was associated with a significant increase in these cytokines [74]. Such works led to the hypothesis that both antibodies, RF and ACPA, may have different pathogenic effects. In particular, RF may induce structural progression via disease activity, activation of mononuclear cells and pro inflammatory cytokines, and through a direct effect on osteoclastogenesis, whereas ACPA may have a direct structural effect on the joint but not on disease activity. The combination of RF and ACPA may lead to the end result of joint damage. Thus, it is possible that although ACPA is not the driving force in RA, it might have a role as a second driver.

5. ACPA as the main biomarker in choosing the therapeutic strategy in RA

5.1. Pros

Biologic disease modifying anti-rheumatic drugs (bDMARDs) have become the standard of care for the treatment of RA not adequately responding to conventional synthetic DMARDs (csDMARDs). The major goal of RA treatments is persistent remission and because of significant interpatient heterogeneity we need to obtain predictors of response and, ideally, of adverse effects for each of these drugs. Therefore, there is huge interest in the field of 'personalised medicine', which should allow us to optimally match patient with treatment, providing the parallel benefit of reduced treatment costs [75,76].

Among bDMARDs treatments, the ACPA status was found to influence mainly treatment response to Rituximab and Abatacept. Indeed, both ACPA and RF were found to predict a good EULAR response to Rituximab therapy and 70% of the seropositive patients responded to the treatment. It should be noted that also 48% of the seronegative patients responded to Rituximab therapy [77]. This association between seropositivity and response to Rituximab is supported by a meta-analysis of four placebo controlled phaseII/III clinical trials. In this meta-analysis there was a statistically significant reduction in DAS ESR at week 24 in seropositive vs seronegative patients treated by Rituximab [78]. These findings were confirmed pooling data from 10 European registries [79].

A prognostic value of ACPA positivity on the response to therapy with Abatacept was seen in an exploratory analysis of the data from the AMPLE Trial. The analysis showed that patients in the highest quartile of ACPA levels responded more favorably to Abatacept compared to ACPA negative patients or patients with lower levels of ACPA. A similar effect was not observed for Adalimumab [80]. Moreover, the ACTION study showed that ACPA positive RA patients have higher rate of good EULAR response to Abatacept compared to ACPA negative and a higher chance of retention rate [81].

Recent data demonstrated that the study of synovial tissue microanatomical organization in RA patients provided evidences that ACPA and/or RF positivity is associated with highly likelihood of presence of synovial follicular structures at disease onset [82] which was demonstrated to be associated with class-switched ACPA production in RA synovium [83]. Moreover, since it has been recently observed that the specific synovial tissue pattern (diffuse vs follicular) could be associated with selective gene signature able to help the stratification of RA patients with high chance of better response specific targeted therapies [84], it might be worth to include ACPA status in the choice of individual therapy mainly in the earliest phase of the disease.

5.2. Cons

Data derived from Ally and coworkers suggested that ACPA level could not be a biomarker able to monitor the efficacy of methotrexate treatment in RA, especially in early disease, despite a significant decline in their titer [85]. Similarly, ACPA failed in predicting the response to anti-TNF treatment. In a study including 30 RA patients treated with Infliximab, the authors observed that the treatment was effective in reducing DAS28 and CRP and decreased RF levels significantly but there was no change in the levels of ACPA at week 78 despite the persistence of clinical improvement [86]. In a large cohort of RA patients in the UK (BRAGCSS group) treated with Etanercept, Infliximab or Adalimumab, the presence of RF or ACPA was associated with a reduced response to anti-TNF drugs. Thus, ACPA positivity in this study was actually a negative predictor for success of treatment [87]. In a meta-analysis testing 10 trials including a large cohort of RA patients treated with anti-TNF therapy, again ACPA had no association with the patient’s response to treatment measured by change in EULAR response, DAS28 or ACR20 [88]. Finally, the BeSt study tested the role of RF and ACPA in predicting the progression of radiographic joint damage with various therapeutic strategies, finding no association between ACPA positivity and the response to the different treatment strategies except for sequential monotherapy. It seems that early and aggressive treatment in RA can prevent joint damage even in patients prone to a more severe damage by interrupting the autoimmune response [89].

Moreover, in an open labeled retrospective non-comparative non-interventional study of seropositive RA patients treated with rituximab for the first time, it has been showed that IgG RF was the only serological biomarker predicting a good response and similarly IgM RF was the only serological biomarker to predict moderate response [90]. The role of ACPA levels in predicting relapse after Rituximab was also tested by Cambridge and coworkers who looked at predictors of response to Rituximab in patients receiving multiple cycles of Rituximab treatment. The patients were thoroughly studied for the changes in B cells, RF and ACPA levels after responding to Rituximab therapy. As expected, B cells were depleted upon clinical response to the treatment in each cycle of treatment and increased prior to the relapse of the disease. However, median levels of autoantibodies remained raised even when patients were in remission. While clinical relapse was associated with the return of B cells, there was no increase in ACPA levels prior to relapse or even during relapse. This confirms that the autoantibodies were not by themselves pathogenic and that ACPA levels could not serve as an indicator for resuming Rituximab treatment [91]. Multiple studies of Tocilizumab treatment in RA did not find a correlation between ACPA positivity and response to treatment [92].

6. Conclusions

ACPAs are more specific than RF for the diagnosis of RA and is an important tool for the diagnostic criteria of RA. It has multiple in vitro effects, mainly on bone, and may predict the development of erosions. However, ACPA even though they improve early RA diagnosis, neither the antigen nor the antibodies have been shown to induce arthritis. As prognostic marker ACPA is associated with increased mortality in RA population mainly due to CV events. Finally, ACPA status is associated with favorable response to b-DMARDs targeting biological pathways directly involving autoantibody producing cells as B lymphocytes but not b-DMARDs inhibiting TNF (Fig. 1). Therefore, despite limitations, the assessment of ACPA status in daily practice seems to provide an additional tool to better stratify RA patients toward “personalised approach” from diagnosis to treatment choice.
ACPA as a driver for RA management?

<table>
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<tr>
<th>PROS</th>
<th>CONS</th>
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<tr>
<td><strong>PRE-CLINICAL &amp; DIAGNOSIS</strong></td>
<td><strong>PROGNOSIS</strong></td>
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<tr>
<td>• ACPA are present in two thirds of RA patients</td>
<td>• ACPA positivity is associated with a severe, erosive phenotype in RA</td>
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<td>• ACPA can be detected years before disease onset</td>
<td>• ACPA positivity is an independent factor of disease flare after treatment tapering/discontinuation in RA patients in remission</td>
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<tr>
<td>• ACPA undergo to Fc fragment glycosylation changes enhancing the inflammatory activity of IgG at the earliest RA phases</td>
<td>• ACPA positivity is associated with higher mortality rate for all causes, mainly cardiovascular</td>
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<tr>
<td>• ACPA positivity is associated with a more favorable response to Rituximab in randomized studies and registries data</td>
<td>• ACPA status does not influence treatment response to TNF-inhibitors in RA patients</td>
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<tr>
<td>• ACPA high positivity identify RA patients with higher chance of Abatacept treatment response</td>
<td>• Despite limited data availability. Tocilizumab response rate seems not to be influenced by the ACPA status in RA patients.</td>
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Fig. 1. Pros and cons about ACPA positivity as a driver for RA management. abbreviations: ACPA: Anti Citrullinated Peptide Antibody; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; DAS: Disease Activity Score; TNF: Tumor Necrosis Factor.

Take-home messages

- ACPAs are specific for RA despite not all patients show the positivity for this biomarker.
- ACPA positive individuals are at high risk of RA development even if they are not arthritogenic by themselves.
- ACPA positivity is associated with a severe erosive phenotype in RA with higher mortality rate for all causes, mainly cardiovascular.
- ACPA status is associated with favorable response to b-DMA RDS targeting biological pathways involving autoantibody producing cells as B lymphocytes.

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