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Biomarkers in Rheumatoid Arthritis

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ABSTRACT: Biomarkers are important for guiding the clinical and therapeutic management of all phases of rheumatoid arthritis because they can help to predict disease development in subjects at risk, improve diagnosis by closing the serological gap, provide prognostic information that is useful for making therapeutic choices and assessing treatment responses and outcomes, and allow disease activity and progression to be monitored. Various biomarkers can be used to identify subjects susceptible to the disease and those with pre-clinical rheumatoid arthritis before the onset of symptoms such as rheumatoid factor and anti-citrullinated protein antibodies. They can be correlated with a risk of developing rheumatoid arthritis and can predict more bone erosions and severe disease progression. Biomarkers such as the erythrocyte sedimentation rate and C-reactive protein levels provide information about disease activity, while predictive biomarkers allow clinicians to assess the probability of a treatment response before starting a particular therapy particularly in the era of biological drugs. This move from traditional approaches to patient stratification and targeted treatment should greatly improve patient care and reduce medical costs.

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KEY WORDS: anti-TNF drugs, biological drugs, biomarkers, rheumatoid arthritis (RA), rituximab

Rheumatoid arthritis (RA), which has an estimated worldwide prevalence in adults of 0.8% and more frequently affects females, is characterized by joint inflammation and destruction and gives rise to functional limitations, working disability, and a poor quality of life [1]. Its etiology is still unknown, and there is increasing interest in studying the biomarkers involved in different stages of this pathogenetically complex disease [2].

A biomarker is an objectively measurable and assessable indicator of normal biological or pathogenic processes or pharmacological responses to a therapeutic intervention [3], which can be derived from genetic polymorphisms, autoantibody profiles, cytokine levels, or clinical parameters. They are divided into three categories distinguished on the basis of their parameters, clinical usefulness, and relation with the pathological process [4]. This last category is further subdivided into descriptive biomarkers (which reflect disease status but are not directly involved in its pathogenesis and provide only limited diagnostic and prognostic information), and mechanistic biomarkers, which are predictively and pharmacodynamically useful as they indicate a dysregulation of the molecular pathways directly involved in disease pathogenesis [5].

Biomarkers are important for guiding the clinical and therapeutic management of all phases of RA because they can help to predict disease development in subjects at risk, improve diagnosis by closing the serological gap, provide prognostic information that is useful for making therapeutic choices and assessing treatment responses and outcomes, and allow disease activity and progression to be monitored [5].

Biomarkers are important for guiding the clinical and therapeutic management of all phases of rheumatoid arthritis

DIAGNOSTIC AND PROGNOSTIC BIOMARKERS

Various biomarkers can be used to identify individuals susceptible to the disease and those with pre-clinical RA before the onset of symptoms. The detection of autoantibodies such as rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs) forms part of the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) diagnostic criteria [6] and can guide the choice of treatments aimed at preventing or slowing the development of symptomatic RA [5]. High RF titers correlate with the risk of developing RA, which may increase by as much as 26 times if they are >100 IU/ml [7], and the presence of the immunoglobulin A (IgA) isotype is associated with extra-articular manifestations [8]. Patients with RF usually develop a more aggressive disease and experience more severe functional impairment. However, RF positivity alone is not sufficient for diagnosis [9] as 15% of the healthy population may have low titers, and this proportion increases with age [10].

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Furthermore, RF is also found in patients with other autoimmune rheumatological or infectious diseases [10,11].

ACPAs develop long before clinical symptoms are noted, and RA patients are divided into ACPA-positive and ACPA-negative [12,13] with characteristics that similar during the early stages of the disease. However, over time, those who are in the ACPA-positive group develop more bone erosions and experience more severe disease progression [13,14]. Environmental factors, especially smoking, can increase the risk of developing ACPAs, and ACPA positivity increases the risk of cardiac disease [15].

A new set of anti-carbamylated protein antibodies, which can be found in ACPA-negative RA patients, has been identified as a potential means of making an early diagnosis and assessing prognosis [16]. They predict joint damage regardless of the presence of ACPAs (which are also known to predict joint damage), as well as the development of early RA [16].

Finally, it has been found that the serum titers of anti-Porphyromonas gingivalis antibodies may correlate with the diagnosis and/or disease activity of RA [17].

MONITORING BIOMARKERS

Biomarkers, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, provide information about disease activity but are not sufficiently predictive alone to be used for purposes of treatment decision making [6,18]. The "treat to target" recommendations include three composite scores for the monitoring disease evolution [19]:

- 28-joint disease activity score (DAS28)
- Simple disease activity index (SDAI)
- Clinical disease activity index (CDAI)

However, as these scores have the disadvantage of the degree of subjectivity of some of their criteria, a multi-biomarker disease activity test has been developed to improve monitoring with mild, moderate and severe disease activity being indicated by scores of 1–28, 29–43, and ≥ 44, respectively [20].

BIOMARKERS PREDICTING TREATMENT RESPONSE

Predictive biomarkers allow clinicians to assess the probability of a treatment response before starting a particular therapy [21]. Major therapeutic advances have been made since the introduction of biological agents targeting pivotal mediators in the inflammatory process by inhibiting tumor necrosis factor alpha (TNF-α inhibitors [TNFIs]), IL-1 (anakinra), IL-6 (tocilizumab), T-cell co-stimulation (CD80/CD86, abatacept), or B-lymphocyte antigen (CD20, rituximab), but 30–40% of the patients receiving biological agents do not respond to the prescribed agent [22].

Predictive biomarkers allow clinicians to assess the probability of a treatment response before starting a particular therapy

The current clinical strategy is to prescribe a biological agent after the failure of initial treatment with methotrexate, often combined with low-dose glucocorticoids. If the decrease in disease activity induced by the first biological agent (usually a TNFI) becomes insufficient (usually after 3–6 months), the patient is switched to another biological agent and the process of evaluating the clinical response is resumed. However, this is very inefficient because the patient may have uncontrolled disease leading to irreversible (and expensive) joint damage [22]. A way to predict responses to specific treatments is therefore needed to optimise the treatment choices for each patient [23].

BIOMARKERS AND ANTI-TNF DRUGS

Many pharmacogenetic studies have so far failed to identify any gene polymorphisms associated with a response to TNFIs [21]. One meta-analysis investigating the role of the TNF-α promoter -308 G/A polymorphism in the response to anti-TNF therapy showed that patients with the G allele responded better, odds ration (OR) = 1.87, 95% confidence interval (CI) 1.26–2.79, and a sub-analysis of RA patients confirmed this result [24].

A recent systematic bioinformatics analysis evaluating the effect of infliximab on refractory RA found that five genes (*FKBP1A*, *FGF12*, *ANO1*, *LRRC31*, and *AKR1D1*) in peripheral blood were associated with efficacy [25]. This model has been shown to have good predictive power in prospective, randomized studies, with an area under the receiver operating characteristic curve of 0.963 and 1.000. It has also been found to be usable in the early phase of treatment (week 2) as a means of predicting response by week 14 (AUC = 1.000). These data suggest that the model is useful for efficiently predicting the response to infliximab in RA patients [25].

Data from the British Society for Rheumatology Biologics Registry (BSRBR) suggest that a poor response to anti-TNF drugs is associated with a high level of baseline disability, that not administering non-steroidal anti-inflammatory drugs or concomitant methotrexate reduces the likelihood of a response (particularly to etanercept), that smokers are less likely to respond to infliximab, and that women are less likely to achieve remission [26]. The Danish DANBIO registry has reported that an older age, prednisolone co-therapy, and poor functional status each predict a poorer response to the first anti-TNF treatment [27], whereas a Gruppo Italiano per lo studio dell'early arthritis (GISEA) study identified RF negativity, a lower Health Assessment Questionnaire (HAQ) score, an age of < 53 years, and male gender as independent predictors of remission at 6 months [28]. The Lombardy Rheumatology Network registry showed that the relative risk (RR) of remission was associated with male gender, and that a lower RR of

remission was associated with previous treatment with > 3 disease-modifying anti-rheumatic drugs (DMARDs), a high ESR, Steinbrocker's functional class III/IV, and a high tender joint count. Futhermore, the same study showed that a 12 month EULAR non-response was observed in 153/821 patients (18.6%) and was associated with a higher baseline HAQ score and previous treatment with > 3 DMARDs (and corticosteroid > 5 mg/day [29]. BSRBR data showed that, after 6 months of anti-TNF therapy (mainly with infliximab and etanercept), RF-positive patients had a DAS28 improvement of 2.43 compared with 3.03 in RF-negative patients ($P = 0.02$), and the equivalent data for ACPA status were 2.40 in ACPA-positive patients, and 2.90 in ACPA-negative patients ($P = 0.02$) [30].

BIOMARKERS AND RITUXIMAB

Studies have found that RF-positive patients respond better to rituximab than RF-negative patients, with ACR20 response values of 54% vs. 41% and 54% vs. 48%, respectively, although a third found no difference between the two sub-groups [31]. Dass and colleagues [32] also found that baseline positivity for circulating ACPA, particularly immunoglobulin M (IgM), and high levels of infiltrating $CD20^+$ and $CD79a^+CD20^-$ B-cells in a rheumatoid synovium predicted an incomplete response after B-cell depletion. A large-scale Italian study comprised of 110 patients found that a lower HAQ score, fewer failures on previous anti-TNF agents before rituximab, and RF (but not anti-CCP) positivity were associated with an ACR50 response, but only RF positivity correlated with a EULAR moderate/good response at both univariate and multivariate analysis [33].

The use of biomarkers should greatly improve patient care and reduce medical costs

The predictors of a better response to rituximab include lower levels of type I interferon (IFN-γ), lower serum levels of B-cell activating factor (BAFF) or B lymphocyte stimulator (BLyS), and a favorable Fcγ receptor III (FcγRIII) genotype [34]. The study also investigated polymorphisms in the promoter region of the BLyS gene, and found that the TTTT BLyS promoter haplotype seemed to be significantly associated with a response to rituximab only in the subset of patients who were seropositive for RF and/or ACPAs and had previously failed on another anti-TNF drug [34]. Finally, the same authors showed that the 158VV Fcgamma receptor 3A genotype is associated with a response to rituximab [35].

BIOMARKERS AND ABATACEPT

The Orencia and Rheumatoid Arthritis (ORA) prospective registry of 1003 RA patients promoted by the French Society of Rheumatology has shown that a EULAR response is associated with anti-CCPA positivity (OR = 1.9, 95%CI 1.2–2.9, $P = 0.007$) but not RF positivity (OR = 1.0, 95%CI 0.6–1.6, $P = 0.9$) [36]. Anti-CCPA positivity is also significantly associated with a higher 6 month abatacept retention rate, a finding that is similar to that reported in clinical trials. Anti-CCPA positivity was associated with a better response to abatacept regardless of disease activity [36].

Furthermore, the large, international, non-interventional ACTION study of a cohort of patients with moderate-severe RA who started intravenous abatacept in Canada and Europe between May 2008 and January 2011 showed that anti-CCPA positivity (hazard ratio [HR] 0.55, 95%CI 0.40–0.75, $P < 0.001$), failure on < 2 previous anti-TNF agents (HR 0.71, 95%CI 0.56–0.90, $P = 0.005$) vs. ≥ 2, and cardiovascular comorbidity at the time of starting abatacept (HR 0.48, 95%CI 0.28–0.83, $P = 0.009$) were associated with a lower risk of discontinuation, and that patients in Greece and Italy were less likely to discontinue abatacept than those in Germany and Canada (Greece HR 0.30, 95%CI 0.16–0.58 and Italy HR 0.50, 95%CI 0.33–0.76; Canada HR 1.04, 95%CI 0.78–1.40; $P < 0.001$ vs. Germany)

The differences in the retention rates may reflect differences in the countries' healthcare systems [37].

In brief, the real-world prognostic factors for abatacept retention include anti-CCPA positivity and fewer prior anti-TNF failures, but not RF positivity.

BIOMARKERS AND TOCILIZUMAB

A multi-center ambispective observational study of 126 RA patients treated with tocilizumab as first- or second-line biological treatment found that the predictors increasing the likelihood of clinical remission after 3 months included a baseline ESR of > 30 mm/h, baseline CRP levels of > 10 mg/L, and the presence of extra-articular disease manifestations, whereas the factors decreasing the likelihood consisted of higher hemoglobin concentrations, a higher baseline DAS28-ESR score, and a higher number of previous DMARDs and biological therapies [38]. There was no relationship with neutrophil counts or RF or anti-CCPA positivity.

FUTURE BIOMARKERS

The use and continued refinement of large-scale genomic, transcriptomic, proteomic, and other "omic" technologies have generated large amounts of multivariate data that require robust bioinformatic analyses, and the candidate biomarkers identified using these data require rigorous validation. Only a few have been adopted in clinical practice. Those that are only detectable in tissue are less useful than those obtained non-invasively [4] and, as RA and other rheumatic diseases are not driven by single gene mutations, single or multiple gene biomarkers are not predictively useful.

Nevertheless, considerable progress has been made by evaluating synovial tissue obtained by means of blind needle biopsies, visually guided arthroscopic biopsies and ultrasound-guided biopsies. The information acquired concerning the

possibility of stratifying patients on the basis of histological patterns may prove to be predictive [39]. It has also been recognised that the microbiome plays an important role in rheumatic diseases such as RA, and the microbial signatures identified by means of next-generation sequencing may lead to a new promising class of biomarkers [4].

Among miRNAs, miR-146a is expressed by activated T cells (in which it suppresses apoptosis and IL-2 production), and its expression in the synovium is associated with increased RA disease activity. Another candidate miRNA biomarker is miR-155, which induces the development of Th1 and Th17 cells, and whose expression is increased in the peripheral blood mononuclear cells of RA patients [4].

CONCLUSIONS

Patients at risk for RA can undergo biomarker tests to detect the earliest stage of disease and begin treatment to prevent its development. The use of predictive biomarkers allows new therapies to be targeted to the patients most likely to respond, and pharmacodynamic biomarkers can be used to monitor their actual response. This move from traditional approaches to patient stratification and targeted treatment should greatly improve patient care and reduce medical costs.

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Capsule

Revisiting annual screening for latent tuberculosis infection in healthcare workers: a cost-effectiveness analysis

In North America, tuberculosis incidence is now very low and risk to healthcare workers has fallen. Indeed, recent cohort data question routine annual tuberculosis screening in this context. Mullie and co-authors compared the cost-effectiveness of three potential strategies for ongoing screening of North American healthcare workers at risk of exposure. The analysis did not evaluate the cost-effectiveness of screening at hiring, and considered only workers with negative baseline tests. Over 20 years, annual screening with the tuberculin skin tests (TST) yielded an expected 2.68 active tuberculosis cases per 1000 workers, versus 2.83 for targeted screening and 3.03 for post-exposure screening only. In all cases, annual screening was associated with poorer quality-adjusted survival, that is, lost quality-adjusted life years, compared to targeted or post-exposure screening only. The annual TST screening strategy yielded an incremental cost estimate of $1,717,539 per additional case prevented versus targeted TST screening, which in turn cost an incremental $426,678 per additional case prevented versus post-exposure TST screening only. With the alternate "higher-risk" scenario, the annual TST strategy costs an estimated $426,678 per additional case prevented versus the targeted TST strategy, which costs an estimated $52,552 per additional case prevented versus post-exposure TST screening only. In all cases, QuantiFERON®-TB (QFT) manufactured by Cellestis Limited, Carnegie, Victoria, Australia was more expensive than TST, with no, or limited, added benefit. Sensitivity analysis suggested that, even with limited exposure recognition, annual screening was poorly cost-effective.

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Eitan Israeli

Capsule

Buprenorphine for the treatment of the neonatal abstinence syndrome

Current pharmacologic treatment of the neonatal abstinence syndrome with morphine is associated with a lengthy duration of therapy and hospitalization. Buprenorphine may be more effective than morphine for this indication. In this single-site, double-blind, double-dummy clinical trial, Kraft and colleagues randomly assigned 63 term infants (≥ 37 weeks of gestation) who had been exposed to opioids in utero and who had signs of the neonatal abstinence syndrome to receive either sublingual buprenorphine or oral morphine. Infants with symptoms that were not controlled with the maximum dose of opioid were treated with adjunctive phenobarbital. The primary endpoint was the duration of treatment for symptoms of neonatal opioid withdrawal. Secondary clinical end points were the length of hospital stay, the percentage of infants who required supplemental treatment with phenobarbital, and safety. The median duration of treatment was significantly shorter with buprenorphine than with morphine (15 days vs. 28 days), as was the median length of hospital stay (21 days vs. 33 days) ($P < 0.001$ for both comparisons). Adjunctive phenobarbital was administered in 5 of 33 infants (15%) in the buprenorphine group and in 7 of 30 infants (23%) in the morphine group ($P = 0.36$). Rates of adverse events were similar in the two groups.

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Eitan Israeli

"Of all the preposterous assumptions of humanity over humanity, nothing exceeds most of the criticisms made on the habits of the poor by the well-housed, well-warmed, and well-fed"

Herman Melville (1819–1891) American novelist, short story writer, and poet of the American Renaissance period