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BIOMARKER-BASED PREDICTION OF THE EFFECTIVENESS OF TREATMENT WITH TNF-α ANTAGONISTS IN RHEUMATOID ARTHRITIS.

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Abstract:

This analytical paper explores how laboratory biomarkers can be used to predict how patients with rheumatoid arthritis (RA) will respond to anti-TNF (anti–tumor necrosis factor) therapy. Rheumatoid arthritis is a long-term autoimmune disorder marked by chronic inflammation, often associated with elevated TNF-alpha levels. Biologic anti-inflammatory medications—such as infliximab, adalimumab, and etanercept—help reduce inflammation and slow disease progression. However, individual responses to these treatments vary significantly. Therefore, biomarkers like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and anti-CCP antibodies play a key role in predicting treatment outcomes. Future studies should aim to further explore, validate, and integrate the most promising biomarkers discussed, as well as identify new potential indicators. Researchers are encouraged to focus on clinical scenarios where predictive models, even with limited accuracy, could meaningfully guide treatment decisions. A comprehensive review of current studies suggests that biomarker-based prediction can support more personalized treatment approaches, help avoid unnecessary drug exposure, and reduce overall healthcare costs.

Keywords: ACR – American College of Rheumatology, CCP – Cyclic Citrullinated Peptide, CRP – C-Reactive Protein, DAS28 – 28-joint Disease Activity Score, DMARD – Disease-Modifying Antirheumatic Drug, ESR – Erythrocyte Sedimentation Rate, EULAR – European League Against Rheumatism, MTX – Methotrexate, RF – Rheumatoid Factor, SJC – Swollen Joint Count, TJC – Tender Joint CountTNF – Tumor Necrosis Factor Inhibitor, VAS – Visual Analog Scale.

INTRODUCTION: When conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) fail to achieve treatment goals in patients with rheumatoid arthritis (RA), current clinical guidelines recommend the initiation of either biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). Among the various bDMARDs available, tumor necrosis factor inhibitors (TNFi) are the most frequently prescribed due to their long-standing use, established efficacy, and favorable safety profile, with more than two decades of clinical experience globally.

Despite their widespread use, studies have shown that many patients either do not respond adequately to the first TNFi therapy or cannot tolerate it. If there is insufficient improvement within 3 to 6 months of starting a bDMARD, clinicians often resort to switching therapies—either to another bDMARD or to a tsDMARD—using a trial-and-error approach. This period of therapeutic uncertainty may result in persistently high disease activity. While glucocorticoids are often used to control symptoms during this phase, they do not prevent the worsening of clinical signs such as pain, fatigue, reduced physical function, or the risk of irreversible joint damage. Additionally, high disease activity and treatment transitions contribute to increased healthcare utilization and associated costs (e.g., consultations, missed workdays, loading doses).Achieving remission or low disease activity early in the treatment process is crucial, as early remission is linked to more sustained disease control over time. It also facilitates earlier dose tapering, potentially reducing drug-related side effects and lowering overall treatment costs. Consequently, the ability to predict individual patient responses to specific therapies has substantial clinical value.Although several reviews in the field of rheumatology have examined the predictive role of biomarkers for bDMARD response, no consistently reliable biomarkers have been identified so far. This highlights the challenge in identifying robust predictive markers—especially those that can add clinically

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relevant value. This study aimed to systematically collect and analyze data on laboratory biomarkers measured before starting TNFi treatment to assess their predictive ability in RA patients over a 3–6 month period. The analysis included human studies involving TNFi therapies such as etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol. Only blood- and urine-based biomarkers were considered to ensure practical applicability in routine care settings; synovial biomarkers were excluded due to their invasive nature and limited use in daily practice.The primary treatment response outcomes were based on standardized disease activity metrics, such as the 28-joint Disease Activity Score (DAS28), and response criteria set by either the European League Against Rheumatism (EULAR) or the American College of Rheumatology (ACR). Studies were included if they met the eligibility criteria or showed potential relevance based on title and abstract review. Full-text articles were retrieved for further evaluation.From each selected study, the following information was extracted: general publication data (authors, title, year), study and participant characteristics (sample size, type of TNFi used, duration of follow-up, disease duration, treatment history, concurrent csDMARD use), biomarker details (type and classification), primary outcome metrics (method of disease activity measurement, response criteria), and results (true/false positives and negatives).Two reviewers (MHMW and BvdB) independently extracted data from a random sample of studies, and discrepancies were resolved through discussion. Once consensus was reached, the remaining data were divided and validated by each reviewer independently. Data collection was performed using a standardized extraction form.To align with clinical decision-making practices, where treatment decisions are typically binary, biomarker outcomes were dichotomized and presented in 2×2 contingency tables. For biomarkers with more than two categories—such as genetic variants—the most commonly referenced variant from the literature was used for consistency. Responses were classified as either "yes" or "no." When using EULAR criteria, moderate and good responses were grouped together when possible, although studies reporting only good EULAR responses were still included. Studies were also included if they reported an absolute DAS28 score of ≤3.2 or an improvement of ≥1.2, as these were considered sufficiently comparable with EULAR criteria. For studies using ACR criteria, ACR50 was the preferred threshold for response. Since ACR20 was considered approximately equivalent to a good or moderate EULAR response, it was accepted as a valid endpoint. However, ACR70 was excluded from the analysis due to its more stringent criteria compared to EULAR definitions. The preferred follow-up duration was six months. When studies reported results at multiple time points, the closest data to six months (i.e., 24 weeks), ranging between 12 and 30 weeks, were included.Five biomarkers were assessed in at least three separate studies: (1) anti-cyclic citrullinated peptide antibodies (anti-CCP), (2) rheumatoid factor (RF), (3) the −308 TNF-α gene polymorphism, where the GG genotype was evaluated as a potential predictor of treatment response, (4) the presence of one or two shared epitope (SE) alleles in the HLA-DRB1 gene, and (5) the FcGR2A gene polymorphism (rs1081274), with the RR genotype considered predictive. These biomarkers were analyzed across 24 unique studies, summarized in Table 2, which included treatments with various TNF inhibitors: etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab.Treatment response in these studies was measured using different outcome metrics: EULAR response criteria (n=14), a relative DAS28 reduction of more than 1.2 (n=5), later response definitions (n=2), ACR50 (n=1), EULAR good response only (n=1), and an absolute DAS28 score greater than 3.2 (n=1). No single study reported a likelihood ratio (LR) greater than 10 or less than 0.1 for any biomarker, and the LRs presented were not adjusted for or combined with other predictive factors.Anti-CCP antibodies were investigated in eight studies. Among them, only one demonstrated a weakly positive correlation with treatment response (LR+ between 2.0 and 10). Five studies suggested a positive association between anti-CCP and treatment effectiveness, while three indicated the opposite. A similar pattern was observed for RF: of nine studies, four found a negative relationship between RF positivity and response, one found no association, and four reported a positive association. These inconsistent findings for both anti-CCP and RF were further supported by multivariable analyses in several studies, which failed to establish statistically significant predictive value when accounting for additional variables.Regarding the TNF-α −308 polymorphism, seven studies examined its predictive value. Six of these found a positive association (LR+ ranging from 1.05 to 1.63) between the GG genotype and a favorable response to etanercept or infliximab, whereas one study reported a negative association between the GG genotype and response to adalimumab. Additionally, four studies evaluated the HLA-DRB1 SE alleles, and three examined the FcGR2A polymorphism. However, none of these showed strong prognostic relevance.In total, 70 additional biomarkers—mostly involving genetic polymorphisms and proteins—were evaluated in

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one or two studies each (listed in Online Supplementary File 4). None of these individual studies reported LRs above 10 or below 0.1. Nonetheless, three biomarkers (each studied only once) exhibited both sensitivity and specificity exceeding 70%, suggesting some potential for clinical application, though requiring further validation.This review also considered composite biomarkers, including elevated granulocyte-macrophage colony-stimulating factor levels (>3.5 pg/ml), high interleukin (IL)-35 concentrations (>194.12 pg/ml), and a combination of high IL-6 levels (>41.59 pg/ml) with low survivin levels (≤780.74 pg/ml). Our analysis focused on laboratory biomarkers that may predict patient response to TNF inhibitors in rheumatoid arthritis (RA).Among the five biomarkers investigated in at least three studies—anti-CCP antibodies, rheumatoid factor (RF), the −308 GG polymorphism in the TNF-α gene, the presence of one or two HLA-DRB1 shared epitope (SE) alleles, and the RR polymorphism in the FcGR2A gene—none demonstrated a likelihood ratio (LR) greater than 10 or less than 0.1. Only one of eight studies examining survivin showed a weakly positive association (LR+ above 2). Moreover, these five commonly studied biomarkers produced inconsistent results across the literature, undermining their reliability as predictive tools.Compared to a previous review by Kuppen et al., our study included a broader selection of research on laboratory biomarkers for predicting TNF-α treatment response. Nonetheless, our findings aligned with theirs, reaffirming that anti-CCP, RF, and the −308 GG TNF-α polymorphism lacked consistent predictive power. Kuppen et al. had highlighted the HLA-DRB1 SE alleles as a potentially useful predictor with an added prognostic value of over 15%, although this was based on a single study. Our review expanded this to four studies but still found only weak associations, casting doubt on its practical relevance.Initially, we anticipated identifying multivariable models composed solely of laboratory biomarkers. While we did find some predictive models, most also incorporated patient characteristics, placing them outside the scope of this review. We deliberately excluded clinical and treatment-related variables due to their limited standalone prognostic significance in influencing treatment decisions. However, this exclusion could be considered a limitation of our review.Only one multivariable model fit our inclusion criteria: a combination of IL-6 and survivin levels. This biomarker pairing demonstrated strong potential, showing a sensitivity of 80% and specificity of 91%, although further studies are needed to replicate and confirm these findings. Our intention was to calculate diagnostic metrics such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and both positive and negative likelihood ratios (LR+ and LR−). These are critical for determining a biomarker's predictive accuracy and reliability. However, strict adherence to these criteria led to the exclusion of 80 studies, mainly due to incomplete reporting. This limitation likely stems from the fact that response prediction was not the primary focus in many of those studies, potentially introducing reporting bias. For practical reasons, we did not reach out to the authors of excluded studies to request missing data, which is another limitation.Nonetheless, we aimed to maximize the likelihood of detecting true effects by applying the most rational observation timeframes. Since no biomarker demonstrated a strong LR association, the risk of misinterpretation affecting our conclusions was minimal.Evaluating the clinical relevance of biomarkers is inherently complex. Any potential prognostic marker should be assessed in terms of whether it offers added value in clinical decision-making. Furthermore, effective predictors should yield consistent and easily accessible test results, be cost-effective, and remain reliable regardless of concurrent treatments. Often, biomarker-based predictions are secondary objectives in broader studies, resulting in limited reporting and lack of validation. While identifying potential predictors in observational cohorts is a logical starting point, it is crucial to include all relevant variables, report predictive metrics clearly, and verify results in follow-up studies.

CONCLUSION: This review offers a comprehensive analysis of laboratory biomarkers evaluated for their potential to predict treatment response to TNF-α inhibitors in rheumatoid arthritis. At present, no single biomarker has demonstrated a significant ability to alter the likelihood of treatment success in a way that would support its use in routine clinical decision-making. Future studies should concentrate on further investigating the most promising biomarkers highlighted in this review, identifying new potential predictors, and exploring the combined use of multiple indicators. It is also essential for researchers to consider the clinical context in which biomarkers are applied, ensure transparent and thorough reporting of findings, and prioritize validation of results through replication.

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