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What is rheumatoid factor? From screening to personalized management

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Abstract

The RF is a representative autoantibody against the crystallizable fragment (Fc) of denatured IgG that is primarily detected in patients with RA. Although five types of TNF inhibitors can be used to treat RA, no guidelines are available for selecting the appropriate inhibitor for treatment. High serum RF levels are associated with high disease activity, progressive joint destruction, life prognosis associated with organ damage, decreased treatment responsiveness to TNF inhibitors and other drugs and low treatment retention rates. Meanwhile, certolizumab pegol (CZP), a TNF inhibitor without the Fc region, remains at high concentrations in the blood. Unlike other antibody drugs with the Fc region, CZP maintains efficacy in patients with high serum RF levels. When serum IgM-RF levels are high, antibody drugs with the Fc region are more likely to bind to IgM-RF and be degraded. Thus, CZP without the Fc region may be more favourable for patients with high serum RF levels.

Keywords: RA, RF, treatment, bDAMRD, certolizumab pegol.

Rheumatology key messages

- High serum IgM-RF levels are associated with high disease activity, joint destruction, decreased responses to TNF inhibitors in patients with rheumatoid arthritis (RA).
- In RA patients with high serum IgM-RF, serum levels of the antibody drugs, treatment responses and retention rate decreased by treatment with TNF inhibitors with the Fc region, whereas they did not change by certolizumab pegol (CZP) without the Fc regions.
- The immune complexes of antibody drug bearing Fc and IgM-RF can bind to the Fcγ receptor of macrophage and be degraded by lysosomes after the internalization into the cells.

Introduction

The RF is a term initially designated in 1939 for the autoantibodies against the crystallizable fragment (Fc) of denatured immunoglobulin (Ig) G that are detected in the serum of patients with RA [1]. Most RFs are IgM antibodies, and ∼70–90% of patients with RA are RF-positive. However, these antibodies are also detected in patients with other connective tissue diseases or liver diseases and healthy individuals. Therefore, the antibodies do not possess high specificity. Nevertheless, RFs are widely used in real-world clinical practice owing to ease of measurement [2]. In the 2010 ACR/EULAR classification criteria for RA, which adopts a scoring system, a condition with a score of 6 points or higher on a 10-point scale is classified as a definite RA. The serum level of RF and anti-CCP antibody has a weight of 3 points according to the serological test [3].

In general, the role of serum biomarkers can be divided into at least three major ones: diagnostic tool, measurement of disease activity and selection of therapeutic tools. Anti-CCP is superior to RF in diagnostic tools. Contrarily, RF is associated with disease activity better than anti-CCP antibody and changes in RF, but not anti-CCP, is modulated by treatment with TNF inhibitors [4, 5]. Serum RF positivity and high RF levels are also used as poor prognostic factors for determining treatment strategies. According to the 2022 EULAR recommendations for the treatment of RA, the addition of a concomitant biologic DMARD (bDMARD) or targeted synthetic DMARD (tsDMARD) is recommended for patients who have failed to achieve remission induction with MTX and have poor prognostic factors, such as positivity for RF or anti-CCP antibody [4]. In fact, joint destruction is well-known to progress more rapidly in RF-positive patients with RA than in RF-negative patients. Patients with high serum RF levels are also considered to have high disease activity and poor life prognosis due to organ damage [5]. Therefore, the pathology of RA can be classified by the detection or concentration of RF in the serum.

In this review, I aimed to present an overview of the association between high serum RF levels and the pathological processes and joint destruction in RA. In addition, I described

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the differences in treatment responsiveness among TNF inhibitors and the mechanisms associated with treatment responsiveness in patients with high RF levels. Finally, I discussed the differential use of TNF inhibitors according to differences in serum RF concentrations, particularly the potential application of precision medicine in RA.

Treatment of RA and new challenges

RA, which is defined as a prolonged destructive arthritis, is an autoimmune disease with multiorgan involvement that manifests with polyarthritis as its primary pathology [3]. Based on the elucidation of the pathological mechanisms of RA, immunosuppressive agents are used to adjust immune abnormalities and control the disease. The immunosuppressive agents used for RA treatment are called DMARD. These drugs can be further classified into conventional synthetic DMARD (csDMARD) such as MTX, targeted synthetic DMARD (tsDMARD) such as Janus kinase (JAK) inhibitors, and biological DMARD (bDMARD) derived from biological agents.

MTX is the initial standard of care for patients diagnosed with RA without contraindications [4]. When the use of MTX fails to achieve improvement within 3 months or remission within 6 months, use of a bDMARD is recommended. If the goal is still not achieved, other appropriate bDMARDs or JAK inhibitors are administered for ∼3–6 months until remission is induced. Such treatment strategies have enabled physicians to induce remission and prevent progression of structural damage and dysfunction of joints in most patients with RA.

At the global level, 9–10 bDMARDs and 3–5 tsDMARDs are available for the molecular targeted therapy currently being administered to patients who do not respond to MTX. However, guidelines for selecting the appropriate molecular targeted drug among them are not available. In actual clinical practice, TNF inhibitors are often the first-choice treatment to balance efficacy and safety given the accumulated results of post-marketing surveillance.

The six TNF inhibitors used at the global level include a chimeric mouse and human antibody (infliximab; IFX), humanized antibodies (adalimumab; ADA and golimumab; GLM), a fusion protein composed of a TNFα receptor and IgG-Fc region (etanercept; ETN), a trivalent anti-TNFα NANOBODY® compound (ozoralizumab, approved in Japan) and polyethylene glycol (PEG) conjugated anti-human TNFα antibody antigen-binding (Fab') fragment (certolizumab pegol; CZP) (Fig. 1). Currently, one of the six TNF inhibitors is often selected based on the experience of the physician. No known criteria are available for selecting the appropriate TNF inhibitor, but several studies have shown lower drug retention with antibody drugs compared with etanercept, hypothetically due to lower anti-drug antibody formation, and certolizumab may be a suitable choice if pregnancy is being considered. The need for precision medicine, in which different molecular targeted drugs are used based on stratification of patients according to their pathological conditions, has been discussed to provide more effective treatments with fewer adverse events.

Association between the pathology of RA and high RF levels

Many attempts have been made to stratify patients according to their pathological conditions. To understand the pathology and evaluate the validity of molecular targets, we collected peripheral lymphocytes from patients with RA, stained their lymphocytes with ∼50 types of antibodies, and analysed the immunophenotypes using multicolour flow cytometry. Although hierarchical cluster analysis of the immunophenotypes enabled the classification of patients with RA into several clusters, significant results that are useful for the differential use of molecular-targeted drugs have not been obtained [6]. Other institutions are investigating the cellular and molecular pathways in the synovium of patients with RA by performing ultrasound-guided synovial biopsy. Based on these investigations, patients with low or absent synovial B cell molecular signatures were found to be less responsive to the anti-CD20 antibody rituximab than to the anti-IL 6 receptor (IL-6R) antibody tocilizumab [7]. In real-world clinical settings, it is challenging to perform a biopsy on every patient and further research is needed to develop simpler methods for patient classification.

The measurement of RF is simple and easy to perform even in actual clinical practice. As described above, serum RF positivity and RF concentration are used as predictors for joint and life prognoses to establish appropriate treatment strategies. The significance of serum RF in disease management has been recognized [2]. Serum RF is detected ∼10 years before the onset of RA, and the presence of RF in combination with genetic and environmental factors is considered to lead to the

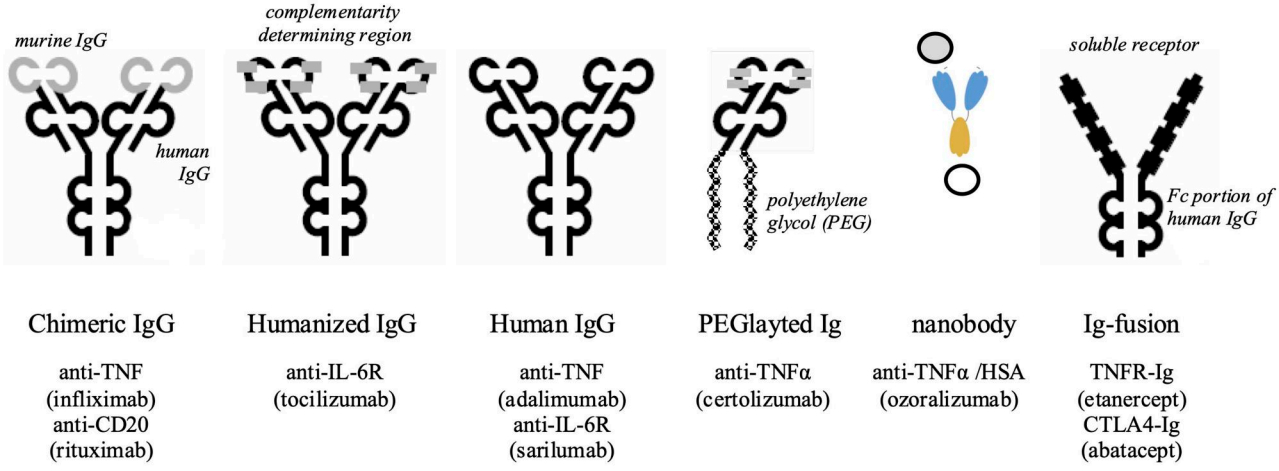

Figure 1. Representative biological agents used for RA

onset of RA [8]. Although the methods for measuring serum RF levels are assumed to be compatible, the definition of high RF levels varies slightly among different studies. Generally, 200 IU/ml or higher may be considered elevated [5, 9, 10].

High serum RF levels are associated with high disease activity, progressive joint destruction, etc. The association between high serum RF levels and progression of joint destruction was investigated in the Active-Controlled Study of Patients Receiving IFX for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) trial comprising patients with early-stage RA who were resistant to MTX and were treated with placebo or IFX [11]. Such association was also assessed in the sub-analyses performed in the Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy (ATTRACT) trial [12]. These trials revealed a clear association between high serum RF levels and progression of joint destruction despite the low degree of progression not only during treatment with MTX but also with MTX and a TNF inhibitor, such as IFX. Interestingly, owing to the analyses performed in these trials, RF, which is a serological marker, and arthritis-associated factors such as CRP, ESR and swollen joint count, were identified as independent factors for the progression of joint destruction. In addition, the combination of RF and arthritis-related factors is associated with further enhancement of the risk [13].

High serum RF levels are associated with concurrent development of vasculitis, organ damage including interstitial lung disease, decreased activities of daily living due to these disorders and poor life prognosis. In fact, high RF and anti-CCP antibody levels have been identified as risk factors for RA-associated interstitial lung disease and RA-associated bronchiectasis [14]. The development of these pathological conditions is assumed to result from stimulations, such as smoking which directly damages the lung, resulting in activation of the immune system. Consequently, the production of autoantibodies and citrullination of protein are enhanced.

In patients with RA, RF positivity is associated with the outcomes and mortality of those with cardiovascular disease, such as ischaemic heart disease, myocardial infarction or heart failure. In particular, patients with high RF levels are at high risk of cardiovascular events and cardiovascular disease-associated mortality [15]. Thus, measurement of RF at the onset of RA is also considered to be useful for predicting cardiovascular events. In patients with high RF levels, the disease activity of RA is high, and consequent atherosclerotic inflammation and endothelial dysfunction may mediate cardiovascular events [16]. However, the details are unknown.

Patients with high serum RF levels from the time of disease onset have poor joint and life prognoses, requiring sufficient therapeutic interventions in the early stages. In contrast, patients with high serum RF levels are likely to be less responsive to TNF inhibitors or experience secondary failure. The development of measures for such patients is urgently required.

Association between treatment responsiveness to TNF inhibitors and high RF levels

High serum RF levels are associated with decreased treatment responsiveness to TNF inhibitors and other drugs, decreased treatment retention rate, high disease activity and progression of joint destruction. By administering a combination of MTX and IFX to treat refractory RA, De Rycke *et al.* found a significant reduction in serum IgM-RF levels at week 30 but no changes in the anti-CCP antibody levels. Furthermore, these investigators revealed that baseline serum IgM-RF levels are inversely correlated with the rates of changes in CRP and ESR after IFX therapy [13]. Thus, patients with high IgM-RF levels are less responsive to IFX.

In the RISING study (Clinical Study to Assess the Efficacy and Safety of Increased Dose of TA-650 [IFX] in Patients with Rheumatoid Arthritis), in which patients resistant to MTX were treated with different doses of IFX (3, 6 and 10 mg/kg), blood IFX concentrations increased more slowly with increasing serum RF levels. In fact, remission was difficult to achieve with 3 mg/kg of IFX in patients with high serum RF levels. Overall, 10 mg/kg of IFX was found to be required to achieve remission [17].

In the REALISTIC trial (RA Evaluation in Subjects Receiving TNF Inhibitor CZP), patients with RA who did not respond to TNF inhibitors received a placebo or CZP and were divided into quartiles based on baseline serum RF levels to evaluate the treatment efficacy. The percentage of patients who achieved a 28-joint disease activity score based on CRP (DAS28-CRP) of <2.6 at week 36 was lower in the placebo group with high RF levels (RF = Q4; the highest quartile) than in the placebo group with low RF levels (RF $\leq$ Q3); however, the levels of RF were not affected in the groups treated with CZP [18].

In the C-OPERA study (Certolizumab-Optimal Prevention of Joint Damage for Early Rheumatoid Arthritis study), MTX-naive patients with highly active RA received MTX in combination with placebo or CZP and were divided into quartiles based on baseline serum RF levels to evaluate treatment efficacy. At week 24, the rates of remission achievement, as defined by the 28-joint disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) and low disease activity, were low in the high RF groups (RF = Q3, Q4) treated with MTX alone. Notably, RF levels were not affected in the groups treated with CZP [10].

Serum RF levels and differences in treatment responsiveness among TNF inhibitors

CZP is a pegylated Fab' fragment of the anti-human TNF antibody that has a molecular weight of ~90 000 [19]. CZP has two methoxy polyethylene glycol molecules that modify a protein composed of 1 molecule of light (L) chain fragment (κ chain) consisting of 214 amino acid residues and 1 molecule of heavy (H) chain fragment (γ-1 chain) consisting of 229 amino acid residues. This drug binds to and neutralizes not only soluble TNF but also membrane-bound TNF. *In vitro*, CZP inhibits monocytes from producing TNF and interleukin 1 (IL-1). Because CZP does not have the Fc region, it does not exhibit cytotoxic activity on TNF-expressing cells. According to pegylation, CZP is less likely to be affected by proteolysis, and its action is expected to persist.

The blood concentration of CZP increases rapidly, and its inflammatory tissue selectivity is high. This drug is considered to exert its effect rapidly. After a single subcutaneous administration of 400 mg of this drug to healthy individuals, its maximum plasma concentration (C_{max}) was 49.5 ± 8.2 μg/m and its half-life was 13.0 ± 2.6 days. Actually, we observed that the mean CZP concentration rapidly increased to 11.3 and 24.2 μg/ml at 24 and 48 h after the first administration of

CZP in patients with RA. Serum TNFα and IL-6 levels significantly decreased from baseline at 24 h after the first administration of CZP in RA patients with inadequate response to methotrexate in TSUBAME study. Moreover, serum levels of CZP at 24 h were strongly and negatively correlated with TNFα levels at 24 h, which were negatively correlated with the improved rate in DAS28 (ESR) at week 12 [20].

By administering any of the three types of TNF inhibitors (IFX, ADA and CZP) to patients resistant to MTX, Martinez-Feito *et al.* found lower blood concentrations of IFX and ADA at 6 months in RF-positive patients with high RF levels than in those with low RF levels. Interestingly, the serum CZP concentrations did not decrease, regardless of RF positivity or high RF levels. Patients with high baseline RF levels dropped out more frequently by secondary non-response in IFX or ADL than CZP (80% *vs* 75% *vs* 33%, $P = 0.002$) [21].

López Medina *et al.* [22] divided 638 patients with RA into quartiles to receive any TNF inhibitor based on baseline RF levels and investigated the treatment retention rate for up to 10 years. Among patients with a serum RF level of 200 IU/ml or higher, the treatment retention rate was significantly higher in those treated with CZP than in those treated with TNF inhibitors including IFX, ADA and ETN. However, no intergroup difference was observed in patients with a serum RF level of <200 UI/ml. This result suggests that RF may affect binding to the fragment crystallizable region of specific TNF inhibitors.

The Phase IV EXXELERATE trial (A Multicentre, Single-blind, Randomized Parallel-group Study to Assess Short- and Long-term Efficacy of CZP Plus MTX Compared with ADA Plus MTX in Subjects with Moderate to Severe Rheumatoid Arthritis Responding Inadequately to MTX) directly compared the efficacy of CZP, a TNF inhibitor without the Fc region, to that of ADA, which has the Fc region, in patients with RA and high RF levels. Following division into quartiles based on serum IgM-RF levels, the patients were classified into the high RF = Q4 and low RF ≤ Q3 groups for analysis. At week 24, the mean DAS28-CRP values in the low RF ≤ Q3 group were comparable between patients treated with CZP and those treated with ADA, whereas the mean DAS28-CRP values in the high RF = Q4 group were lower in patients treated with CZP than in those treated with ADA (Fig. 2) [10]. A similar trend was observed at week 104, mean DAS28-CRP was similar between CZP- and ADA-treated patients through week 104 for patients with RF ≤ 204 IU/ml, whereas it was lower in CZP- *vs* ADA-treated patients at week 104 for patients with RF > 204 IU/ml and the proportion of patients with RF > 204 IU/ml achieving DAS28-CRP low disease activity at week 104 was greater in CZP- *vs* ADA-treated patients [23]. Regardless of the anti-citrullinated peptide antibody levels, DAS28-CRP values were comparable between patients treated with CZP and those treated with ADA. Serum ADA concentrations tended to decrease in the high RF = Q4 group, whereas serum CZP concentrations were comparable in all groups. These results suggest that, unlike ADA, CZP remains at high concentrations in the blood and is even effective in patients with high RF levels.

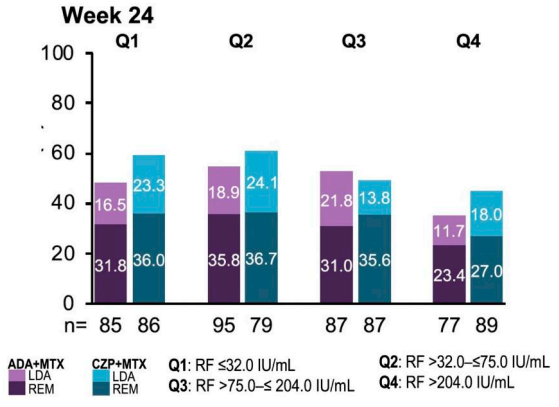

Figure 2. Efficacy of certolizamub pegol across serum levels of RF at baseline of subgroups in patients with RA, post-hoc analysis of a clinical trial EXXELERATE, from Ref. [10]

Binding of antibody drugs to IgM-RF and their clearance

In the pathogenesis of RA, when self-tolerance is disrupted by some factor, autoreactive T cells are activated and B cells are stimulated to induce the production of autoantibodies. The RF is an autoantibody that recognizes the Fc region of other IgG detected in RA and other conditions. Most RFs are IgM-RF and IgA-RF, which bind to the Fc region of IgG. RFs do not bind to native IgG present in the body. However, IgM-RF can bind to IgG when IgG binds to a ligand, such as TNFα, via Fab' fragment or when the Fc region is exposed after conformational changes due to specific physicochemical stimulation (Fig. 3) [24–27].

During treatment with antibody drugs, anti-drug antibodies often appear and change the pharmacokinetics. Consequently, the concentrations of antibody drugs and their therapeutic effects are reduced. Anti-drug neutralizing antibodies competitively inhibit the binding of antibody drugs to target antigens. In contrast, conjugated anti-drug antibodies bind to the Fc region of antibody drugs to form immune complexes [28]. These immune complexes bind to the Fcγ receptor of macrophage and are engulfed by cells, where the antibody drugs and others are degraded by lysosomes. Thus, the immune complex of antibody drugs and anti-drug antibodies are degraded in lysosomes, suggesting that antibody drugs bind to IgM-RF and the complexes can be degraded via similar mechanisms.

According to comprehensive consideration of these mechanisms, many antibody drugs undergo conformational changes when bound to antigens (ligands or TNFα for anti-TNFα antibodies). Thereafter, the Fc region is exposed, enabling binding to IgM-RF. Antibody drugs binding to IgM-RF bind to the Fcγ receptor of macrophages, are internalized into cells, and are degraded by lysosomes. Such a mechanism is generally applicable to antibody drugs with the Fc region.

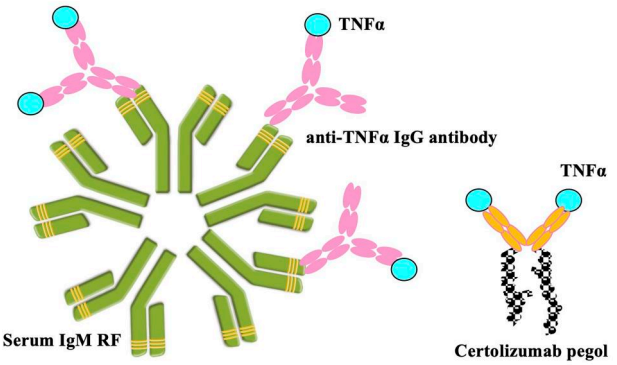

Figure 3. Interaction between RF and IgG antibodies

If the serum IgM-RF level is high, a larger amount can bind to IgM-RF and ultimately be degraded. When patients with RA and high serum RF levels are treated with TNF inhibitors with the Fc region, serum concentrations of the antibody drugs, their efficacy and treatment retention rate decrease. However, these trends are not observed during treatment with CZP, which does not have the Fc region. The lack of such a trend may be attributable to this mechanism [25–27].

The presence or absence of the Fc region in antibody drugs is also associated with placental transfer. The active transfer of IgG antibodies across the placenta is initiated in the second trimester via their binding to the foetal Fc receptor (FcRn) expressed in the placenta. IgG, including antibody drugs, binds to FcRn expressed in the maternal circulation via the Fc region and is transported to the placenta. Thereafter, IgG is recycled from endosomes for release into foetal circulation [29, 30]. In fact, biological agents, such as ADA, are detectable in approximately half of the umbilical cord blood samples from patients; however, transfer of CZP is rarely observed.

Conclusion

Multiple types of effective molecular targeted drugs have been approved for rheumatic diseases, such as RA. New treatment systems, including differential use of the drugs, are essential. Optimization of molecular targeted therapy according to pathology is an especially important issue in autoimmune diseases with high clinical and molecular cytological heterogeneity. Accordingly, personalized medicine, in which optimal drugs are selected for each patient, is necessary but is limited by its application, cost, etc. In 2015, the then-President of the United States, Barack Obama, proposed the concept of precision medicine for cancer in his State of the Union address. Precision medicine aims to establish therapeutic and preventive strategies for each subgroup of the disease identified based on an analysis of remarkable amounts of biological information data, such as the genome. Treatment specific to subgroups was expected to be realistic in terms of application and cost. Such precision medicine can only be achieved through molecular targeted therapy and should be applied to autoimmune diseases with high heterogeneity. Here, CZP may be selected for use in the 1/4 patient subpopulation with particularly high IgM-RF values. However, the evidence is not sufficient and needs to be validated in patients in routine practice.

In summary, high serum levels of RF in patients with RA are associated with poor joint and life prognoses and reduce treatment responsiveness to TNF inhibitors with the Fc region. Unlike other TNF inhibitors, CZP, which is a bDMARD without the Fc region, is associated with a high treatment retention rate and high efficacy even in patients with RA and high serum RF levels. The differential use of TNF inhibitors aims to achieve high efficacy and a high treatment retention rate by classifying patients with RA into 2 groups based on serum RF levels (i.e. precision medicine for patients with RA).

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request and after ethics application.

Contribution statement

Substantial contributions to review conception, interpretation of reviewed literature, drafting the article, revising it critically for important intellectual content, and final approval of the version of the article to be published: Y.T.

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