C-reactive protein and implications in rheumatoid arthritis and associated comorbidities

Janet E. Pope\textsuperscript{a}, Ernest H. Choy\textsuperscript{b,}\textsuperscript{*}

\textsuperscript{a}Janet E. Pope: Schulich School of Medicine, University of Western Ontario, St. Joseph’s Health Care, London, ON, Canada
\textsuperscript{b}Ernest H. Choy: Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff, United Kingdom

\begin{abstract}
C-reactive protein (CRP) is routinely assessed as a marker of systemic inflammation in rheumatoid arthritis (RA). However, it is also an immune regulator that plays an important role in inflammatory pathways associated with RA and promotes atherogenic effects. Comorbidities linked to systemic inflammation are common in RA, and CRP has been associated with the risk for cardiovascular disease, diabetes, metabolic syndrome, pulmonary diseases, and depression. The relationship between systemic inflammation, CRP, and comorbidities in RA is complex, and it is challenging to determine how changing CRP levels may affect the risk or progression of these comorbidities. We review the biological role of CRP in RA and its implications for disease activity and treatment response. We also discuss the impact of treatment on CRP levels and whether reducing systemic inflammation and inhibiting CRP-mediated inflammatory pathways may have an impact on conditions commonly comorbid with RA.

\textcopyright{} 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
\end{abstract}

Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated systemic inflammatory disease characterized by chronic synovial inflammation and hyperplasia, which drive joint erosion and damage, and a range of systemic manifestations, which contribute to overall disease burden [1]. This results in functional decline, disability, and reduced quality of life for patients with RA, particularly due to symptoms such as pain, fatigue, and morning stiffness [1–5]. Comorbidities are common in RA and require a holistic management approach, as multiple comorbidities are associated with poorer clinical outcomes [6–8]. Patients with RA have an almost 2-fold higher cardiovascular (CV) risk than the general population, [9,10] and more than 50% of premature deaths among RA patients are due to CV disease (CVD) [11].

Proinflammatory pathways result in localized joint and systemic inflammation, [1] with cytokines, such as interleukin-6 (IL-6), tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), IL-1\(\beta\), as well as downstream signalling pathways, eg, the Janus kinase (JAK)/signal transducers and activators of transcription pathway, playing important roles [1,12,13]. One function of IL-6 is to drive production of the acute-phase reactant C-reactive protein (CRP) following an inflammatory event [14–16]. While CRP is a key marker of systemic inflammation in RA, its overarching role in RA and its association with comorbidities has not been comprehensively investigated. In this narrative review, we discuss the role of CRP in RA, focusing on the relationship between CRP and comorbidities, and the effect of RA treatment on CRP levels and outcomes. Articles were identified in PubMed using search terms CRP and RA together with: comorbidity, anaemia, asthma, cancer, chronic obstructive pulmonary disease (COPD), CVD, diabetes, interstitial lung disease (ILD), disease-modifying anti-rheumatic drug (DMARD), methotrexate, TNF inhibitor (TNFi), IL-6, JAK inhibitor, and steroids. Results were limited to articles in English published in the last 10 years and supplemented by inclusion of relevant citations found within identified articles.

Roles of CRP in RA

In general, CRP plays an important role in host defence mechanisms against infectious agents and in the inflammatory response. [17,18] CRP binding to immunoglobulin Fc gamma receptors (Fc\(\gamma\)R) promotes the production of proinflammatory cytokines leading to an amplification loop of inflammation [27–29]. It is produced predominantly by hepatocytes in response to stimulation by IL-6, [14,15] but CRP has also been reported to be expressed by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes (Fig. 1) [18]. A significant correlation has been seen between serum CRP levels and tissue inflammation scores from knee synovium biopsy samples in patients with RA (\(n = 197; p < 0.0001\)) [46]. Analyses of serum
Serum CRP levels can be tested using standard or high-sensitivity (hsCRP) assays; hsCRP is also known as native CRP. It is thought to act as an hepatocyte and secreted into the circulation as pentameric CRP (pCRP). Various isoforms with different biological properties provided a potential explanation for conflicting observations [24]. CRP is synthesized in hepatocytes and secreted into the circulation as pentameric CRP (pCRP), also known as native CRP. CRP is thought to act as an immune regulator [25]. When bound to cell membranes or liposomes, pCRP can irreversibly dissociate via a conformationally changed intermediate into monomeric CRP (mCRP), which is a proinflammatory isoform able to activate platelets, leucocytes, and endothelial cells as well as bind complement component 1q to activate complement [18,25,26]. mCRP has limited solubility compared with pCRP and is considered to be tissue bound, although transmission via microparticles and lipid complexes has been postulated [25]. Depending on its structural form, CRP interacts with a variety of leucocytes and endothelial cells, stimulating proinflammatory cytokine release, including IL-6, IL-1β, and TNF-α, upregulating adhesion molecules, increasing monocyte chemotactic protein-1 release to recruit monocytes, inhibiting nitric oxide production, and activating platelets, thereby inducing proinflammatory and atherogenic effects [Fig. 1] [18,24,26–30]. Reference to CRP hereafter signifies circulating CRP without distinction between isoform unless specified.

### Circulating CRP levels

In healthy adults, plasma CRP concentration is usually <10 mg/L, although there is considerable inter-individual variability [17,18,31,32]. CRP levels >10 mg/L are generally considered elevated, although the normal reference range can differ between assays [33]. Obesity is associated with elevated CRP levels [34]. Serum CRP levels can be tested using standard or high-sensitivity (hsCRP) assays; hsCRP is used for evaluation of conditions potentially associated with inflammation in otherwise healthy individuals [33]. CRP levels are often persistently elevated in patients with RA, with levels of >20 mg/L frequently reported at baseline in randomized clinical trials (RCTs) of drugs to treat RA [35]. However, retrospective and observational real-world studies show that many patients have normal CRP levels despite exhibiting RA disease activity, [36,37] suggesting that CRP levels reflect only one of the signs of disease activity and should be assessed in the context of other measures. Additionally, multiple factors influence baseline serum CRP levels in patients with RA. Single nucleotide polymorphisms in CRP and their haplotypes have been associated with higher or lower CRP levels, although no association was found in a prospective observational study of a patient population with much higher average baseline CRP levels (34 mg/L) [41]. Body fat, female hormone levels, dietary quality, and stress have also been shown to influence CRP levels in patients with RA [42–45]. As pharmacological treatments for RA reduce systemic inflammation, CRP levels generally decrease with treatment, to differing degrees depending on the drug class and mechanism of action.

### Biological effects of CRP in RA

There is growing preclinical evidence that CRP may play a direct role in bone destruction in RA. Bone destruction is initiated via induction of receptor activator of nuclear factor-κB ligand (RANKL) expression, which stimulates osteoclastogenesis, resulting in bone resorption. CRP induces RANKL expression in peripheral blood monocytes and stimulates osteoclast differentiation in the absence of RANKL [20]. However, the effects of CRP on osteoclast differentiation might depend on CRP isoform. mCRP has been shown to inhibit RANKL-induced osteoclast differentiation in vitro, by neutralizing RANKL, potentially exerting a protective effect [47,48]. Additionally, patients with RA who have a monocyte imbalance (M1/M2 ratio >1) exhibit significantly higher levels of CRP than those with M1/M2 ratio

---

**Fig. 1.** The biological role of C-reactive protein (CRP). C1q, complement component 1q; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; mCRP, monomeric CRP; MCF-1, monocyte chemotactic protein-1; NO, nitric oxide; pCRP, pentameric CRP; RANKL, receptor activator of nuclear factor-κB ligand; ROS, reactive oxygen species; TNF, tumour necrosis factor; VCAM-1, vascular cellular adhesion molecule-1.
<1 (4.5 versus 0.8 mg/L; p = 0.032) and greater in vitro osteoclastogenesis [49]. More research is needed to fully elucidate the role of CRP in bone destruction.

**CRP as a marker of RA disease activity**

Higher CRP levels are associated with greater RA disease activity based on the core components of the 28-joint Disease Activity Score (DAS28) [50,51]. Individual aspects of disease activity, such as swollen joint count, and patient-reported measures, including functional status (Health Assessment Questionnaire score), morning stiffness, fatigue, and pain, have also been associated with CRP [52–56]. Indeed, CRP levels are widely used for monitoring systemic inflammation and disease activity in RA. CRP level is a component of several composite disease activity measures: DAS28-CRP, SDAI, and American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) definitions of remission [57–59]. Yet, the usefulness of CRP testing as a routine measure of RA disease activity is not universal due to the substantial proportion of treated patients who experience flares in their RA but still have normal CRP levels. In fact, as RA clinical trials often specify elevated CRP (for example ≥6 mg/L) [60] as an eligibility criterion, patients with active RA but without elevated inflammatory markers are commonly excluded.

Along with disease activity, CRP is known to be associated with radiological damage in RA. Numerous studies in patients with early RA have shown that elevated CRP levels both at baseline and using time-integrated measures correlate with rapid radiological progression and joint damage within 1 year. [61–66] Elevated baseline CRP levels are also a more general predictive factor for radiographic progression and joint destruction in patients with early, moderate and severe RA [64,67,68]. However, a CRP threshold level that could be used as a marker for radiographic progression has not been established.

As noted above, CRP is a standard component of many RA composite disease activity measures (DAS28-CRP, SDAI, ACR/EULAR remission) [57–59]. ACR and EULAR recommend DAS28 using either CRP or erythrocyte sedimentation rate (ESR) without differentiating between them in terms of disease activity thresholds [57]. However, there is evidence that DAS28-CRP scores are consistently lower than DAS28-ESR values [187–189]. Given disease activity thresholds (high >5.1, low disease activity [LDA] <3.2, and remission <2.6) were originally validated using DAS28-ESR, using the same thresholds for DAS28-CRP may underestimate residual disease activity [187,189]. Consequently, new disease activity thresholds for DAS28-CRP of >4.6, <2.9, and <2.5 have been proposed. [187,189] Additionally, there may be challenges in assessing remission with DAS28-CRP when patients are treated with IL-6 inhibitors and other drugs that directly affect levels of CRP, as a reduction in CRP may not reflect a decrease in disease activity. Thus, a more stringent threshold for DAS28-CRP remission of <1.9 has been proposed [190]. Moreover, many patients with active RA may not have an elevated CRP and this is a common reason for screen failures in RA treatment trials [36,191].

**Association of CRP with comorbidities in RA**

There is a high prevalence of comorbidities in patients with RA, the most common of which include CVD, metabolic syndrome, diabetes, pulmonary diseases, and depression [6]. While the biological relationships between CRP levels and comorbidities in RA have not been fully established, elevated CRP levels have been shown to be associated with an increased risk for several common comorbidities (Fig. 2). Understanding these associations is important from a clinical perspective to help in the identification of patients at risk for comorbidities, especially those that may be associated with an increased risk for mortality.

**Cardiovascular comorbidities**

Data from large observational cohorts have shown that RA is associated with an up to 2-fold increased CV risk compared with the general population, [9,10,69,70] including reported increased risks of myocardial infarction (MI; 33–96%), [70–72] heart failure (61–87%), [70,72] stroke (24–29%), [71] and major adverse CV events (MACE; 30–58%), [71,73] along with a 50% higher incidence of CV-related mortality, [71,74] independent of traditional CV risk factors. In a meta-analysis, the relative risk for patients with RA to develop CVD was age dependent, with higher CV risk seen in patients aged <50 than 50–65 or >65 years (risk ratio (RR) 2.59, 1.86, and 1.27 versus the general population) [75]. Moreover, there is evidence from epidemiological studies of a strong association between CRP and IL-6 levels and CV risk. [76–79] In the general population, CRP is considered an independent predictor of CV risk, [80,81] with a 58% increased risk for coronary heart disease with CRP levels >3.0 versus <1.0 mg/L.

---

**Fig. 2.** The interplay of C-reactive protein (CRP) and common comorbidities in RA.

CRP, C-reactive protein; HBV, hepatitis B; HCV, hepatitis C; ILD, interstitial lung disease; MACE, major adverse cardiovascular event; MI, myocardial infarction; RA, rheumatoid arthritis.
[80], CRP is also a predictor of CV risk in RA. Large observational cohort studies have reported associations between elevated CRP levels in RA and a more atherogenic lipid profile and hyperlipidaemia, [83,84] an increased risk for MI (hazard ratio [HR] 2.12, 95% CI 1.02–4.38 for CRP > 10 versus < 1 mg/L), [85] heart failure (HR 1.25, 95% CI 1.06–1.48 per 100 mg/L increase in CRP), [86] stroke (HR 2.02, 95% CI 1.32–3.08 for CRP > 21.7 mg/L versus < 2.6 mg/L), [87] and CV-related death (14% increase for each mg/L and HR of 3.3 [95% CI 1.4–7.6] for CRP ≥ 5 mg/L) [88,89]. Higher CRP levels also increase risk for atherosclerosis and increase subclinical atherosclerosis as measured by carotid intima media thickness in patients with RA [90–94].

Systemic inflammation is a key driver of atherosclerosis. Specifically, CRP has been shown to have a direct biological role in the development and progression of atherosclerosis and thrombosis [82]. CRP increases during the progression of atherosclerosis and can activate the complement system, inducing apoptosis, and contributes to endothelial dysfunction by inhibiting nitric oxide and upregulating endothelial cell adhesion molecules. It also promotes monocyte recruitment into atherosclerotic plaques and increases the inflammatory response by inducing leucocyte adhesion and migration and generation of reactive oxygen species (Fig. 1). CRP also contributes to plaque instability by inducing metalloproteinase expression and promotes thrombus growth via induction of platelet activation.

A reduction in disease activity in RA has been shown to be associated with a reduction in CV risk in numerous studies. Indeed, data from the longitudinal CORRONA registry demonstrated that a 10-point reduction in time-averaged CDAI was associated with a 21% decrease in CV risk [95]. In a meta-analysis of clinical studies, methotrexate and TNFis each appeared to reduce the CV risk by approximately 30% (RR 0.72, 95% CI 0.57–0.91, p = 0.007 and RR 0.70, 95% CI 0.54–0.90, p = 0.005, respectively) [96]. Abatacept showed a modest reduction in risk for a composite CV endpoint compared with TNFis in a large population-based RA cohort (HR 0.86, 95% CI 0.73–1.01) [97]. Despite the known effect of IL-6 inhibitors for increasing lipid levels, [98] in the randomized, open-label ENTRACTE trial, the estimated risk for MACE was similar between tocilizumab (an IL-6R inhibitor) and etanercept (HR 1.05, 95% CI 0.77–1.43) [99]. Likewise, an integrated safety analysis of clinical trials of the IL-6R inhibitor, sarilumab, reported exposure-adjusted incidence rates of MACE of 0.2–0.5/100 patient-years, comparable to the incidence in the general RA population (1.2/100 patient-years) [100]. Pooled safety analyses for JAK inhibitors report similar incidence rates of MACE for tocilizumab of 0.4/100 patient-years and baricitinib (4 mg) of 0.8/100 patient-years. [101,102] Further research is needed to determine whether the biological link between elevated CRP in RA and in CVD and the reduction in CRP levels during treatment for RA contributes to the reduction in CV risk reported in these studies.

### Metabolic syndrome

The prevalence of metabolic syndrome appears to be greater in patients with RA than the general population, with rates of 30–40% reported compared with about 20% in controls [103–107]. Higher CRP levels have been associated with increased prevalence of metabolic syndrome in RA, [107,108] greater abdominal adiposity, [109] decreased insulin sensitivity, [110–114] and increased lipid levels [83]. However, two North American cross-sectional cohort studies did not find a significant association between CRP and metabolic syndrome in patients with RA (odds ratio [OR] about 1 in both studies). [103,106] CRP levels have been associated with lipid abnormalities, [77,115] negatively correlating with high-density lipoprotein cholesterol (HDL-C) [116]. However, a direct biological link between CRP levels and metabolic syndrome in RA has yet to be established.

Conventional synthetic DMARDs (cDMARDs), targeted synthetic DMARDs (tsDMARDs), and bDMARDs all increase lipid levels, [117–121] but TNFis improve insulin resistance and sensitivity, [122–124] and tocilizumab does not appear to significantly affect body mass index, waist circumference, or atherogenic index [118,125], so the overall impact of RA treatments on metabolic syndrome is, as yet, not firmly established.

### Diabetes

Patients with RA are up to twice as likely to be diagnosed with diabetes mellitus (DM) than are the general population, [126–128] and the prevalence of DM in RA is about 13–20%. [6,126,129] Higher CRP levels have been seen in RA patients with type 2 diabetes (T2DM) compared with those without [126]. High CRP levels in RA have also been correlated with impaired glucose tolerance and metabolism and to insulin resistance, [130] and are significantly associated with small increased likelihood of impaired fasting glucose (OR 1.02, 95% CI 1.001–1.034, p = 0.02) [128]. Significant positive associations between the homeostatic model assessment of insulin resistance and CRP and IL-6 levels have also been seen in patients with RA. [111,113,114] However, as for metabolic syndrome in RA, no direct biological link between CRP levels and diabetes in patients with RA has yet been established.

There is evidence that treatment with DMARDS may reduce the risk for T2DM, [131–133] and reduce glycosylated haemoglobin levels (HbA1c) [134] in patients with RA. In the CORRONA registry, treatment with TNFis significantly reduced the risk for T2DM (OR 0.35, 95% CI 0.13–0.91, p = 0.03), while other bDMARDs (OR 0.44, 95% CI 0.08–2.57, p = 0.36), methotrexate (OR 0.67, 95% CI 0.44–1.02, p = 0.34), and hydroxychloroquine (OR 0.45, 95% CI 0.13–1.53, p = 0.21) numerically reduced the risk for T2DM versus patients treated with other csDMARDs [133]. In contrast, the risk for T2DM escalates with increasing doses of glucocorticoids (HR 2.33, 95% CI 1.68–3.22, p = 0.02 for patients using ≥7.5 mg glucocorticoid versus no glucocorticoid) [133]. In a retrospective analysis in Japan, HbA1c levels significantly decreased after 3 months of treatment with either TNFis or tocilizumab (p < 0.001 for both treatments) in patients with RA, including in the subgroup of patients with DM. In this analysis, tocilizumab was associated with greater reductions in HbA1c levels than were TNFis (OR 5.59, 95% CI 2.56–12.2, p < 0.001) [134]. In a post-hoc analysis of sarilumab phase III trials, patients with RA and diabetes had greater improvements in HbA1c with sarilumab 200 mg every 2 weeks (q2w) than with adalimumab 40 mg q2w (−0.43 versus −0.02 at 24 weeks) or placebo (−0.60, −0.33, and 0.18 at 24 weeks for sarilumab 200 mg, 150 mg, and placebo q2w, respectively) [135]. Given the prevalence of DM in RA, the decrease in risk for T2DM and improvements in HbA1c levels with different DMARD treatments should be considered when personalizing RA treatment.

### Pulmonary disease

RA is associated with a 70–100% increased risk for COPD compared with controls, [136–139] and the prevalence of COPD among RA patients is about 4–8%. [6,137,138] COPD has been shown to increase the risk for mortality almost 3-fold in patients with RA. [140,141] High CRP levels have been associated with increased risk for COPD, [142] and higher CRP levels are seen in patients with stable COPD than controls [143,144]. As COPD exacerbations are often caused by infections, the finding that CRP levels are significantly higher in patients with acutely exacerbated versus stable COPD (p < 0.05) is not surprising [144]. In the USA NHANES survey, elevated CRP (>10 mg/L) was associated with increased risk for mortality (HR 4.45, 95% CI 1.91–10.37) in patients with COPD, [145] and a separate analysis showed that CRP ≥ 3 mg/L was associated with increased mortality (HR 1.61, 95% CI 1.12–2.30) [146]. CRP levels ≥3 mg/L in stable COPD are associated with poor predicted forced vital capacity and patient-reported health status [147,148].
Data on the effects of RA treatments on COPD are limited, but due to more frequent respiratory adverse events seen among patients with COPD in the ASSURE trial, the risk for COPD exacerbations with abatacept has recently been described [149]. In retrospective population-based cohort studies of patients with RA and COPD, abatacept was not associated with significantly increased risk for COPD exacerbation or respiratory adverse events compared with csDMARDs, tsDMARDs, TNFis, or other bDMARDs [150,151]. Data from RCTs for patients with RA and comorbid COPD would be valuable to further investigate the effects of DMARD treatment to determine whether reducing the generally higher CRP levels seen in patients with RA may impact positively their COPD.

The lifetime risk for patients with RA developing ILD has been reported at 6–15%, compared with 1% for the general population [152,153]. ILD may occur before the development of articular manifestations in RA [152,154,155]. A population-based study in Denmark found that 14% of ILD cases in patients with RA were diagnosed 1–5 years before RA diagnosis, and 34% within 1 year prior to and 1 year after RA diagnosis [155]. Pulmonary abnormalities compatible with ILD were present in 21/36 patients (58%) with recent onset RA (duration of joint symptoms <2 years) who were referred to a university rheumatology department [156]. The main risk factors for developing RA-ILD are smoking, older age, male sex, rheumatoid factor, and anti-cyclic citrullinated peptide antibody levels [154,157]. Of the RA-ILD subtypes, usual interstitial pneumonia (UIP) is generally the most common, followed by non-specific interstitial pneumonia (NSIP) [157,158]. RA-ILD is associated with poor prognosis, with hazard rate ratios for death 2–10 times higher in RA-ILD than in RA without ILD [159]. Patients with a UIP histological pattern have the worst prognosis, with mortality rates similar to those observed among patients with idiopathic pulmonary fibrosis [159–162]. It is uncertain if high CRP is related to progression of ILD in RA. Although higher CRP levels in patients with RA-ILD versus RA without ILD have been observed in several retrospective studies in Asia, [163–165] this pattern was not seen in an Italian retrospective study [166]. Additionally, the association of high CRP levels with risk for ILD was not significant in a multivariate analysis in Chinese patients, suggesting that CRP level may not be an independent risk factor for ILD [163].

Depression

Depression is highly prevalent in patients with RA, with a reported prevalence of 15–40%, and it is more common in patients with RA than in the general population [6,167]. Elevated CRP, TNF-α, and IL-6 levels have been noted in some studies in RA patients with depression [168,169]. Elevated CRP has been associated with higher depression scores in patients with RA [170–172]. However, the association between systemic inflammation and depressive symptoms is complicated by factors such as pain and disease activity, which may attenuate the link between CRP and depression [170–172].

The relationship between depression and treatment response in RA appears to be bidirectional. In the CARDERA RCT in patients with early RA who received methotrexate or methotrexate plus prednisolone and/or cyclosporine, patients reporting persistent depression/anxiety were significantly less likely (62–90%; p < 0.05) to achieve clinical remission (DAS28 <2.6) over 2 years [173]. In a large UK observational study, depressive symptoms at baseline did not predict non-response to methotrexate after 6 months of treatment [174]. Additionally, compared with RA patients without depressive symptoms, patients with RA but no depressive symptoms at baseline who responded to TNFi treatment were 20% less likely to develop depression than were non-responders (7.1% versus 9.4%; p < 0.005; adjusted OR 0.80, 95% CI 0.64–0.98) [176]. Etanercept has also shown small but significant effects (7–28%) in reducing depression scores compared with methotrexate in patients with RA [177]. Analyses of patient-reported outcomes in phase III trials in RA showed improved Mental Health and Role Emotional domain scores of Short Form 36 with sarilumab, tocilizumab, and tofacitinib [178–180]. Further, in an interim analysis of the ARATA study of tocilizumab treatment in routine practice, tocilizumab improved depressive symptoms over 2 years, [181] and in the ACT-AXIS prospective observational study, tocilizumab significantly decreased depression score (p < 0.005), [182] Given the complex interplay of depression with RA disease activity, inflammation, and RA symptoms, poorer RA treatment outcome may be influenced, at least in part, by presence of depressive symptoms [183].

Clinical implications of CRP in the management of patients with RA

Circulating CRP level is routinely tested, as it is an inexpensive and readily available biomarker to assess systemic inflammation and clinical outcomes in RA. CRP levels can be assessed via standard or hsCRP assays, with values <10 mg/L and <1 mg/L, respectively, generally considered normal, although thresholds may differ between assays [33,184]. In RA, given the generally elevated levels of CRP due to systemic inflammation, the hsCRP assay is typically considered unnecessary. There are limitations of conventional CRP testing: for the substantial proportion of patients who have normal CRP levels while exhibiting RA disease activity or flare, [36,37] a low CRP level may provide false reassurance of reduced inflammation. Additionally, while CRP is a marker of systemic inflammation, it is not useful as an independent factor for predicting the risk for developing RA, [185,186] and it does not confirm a diagnosis of RA. In the context of comorbidities in RA, a specific CRP level/threshold is not a predictor for any particular comorbidity.

Screening for CV risk factors in patients with RA

Given the increased morbidity and mortality associated with CVD in RA compared with the age- and gender-matched population, CV risk should be assessed for all patients [192]. General CV risk calculators, such as SCORE and the Framingham risk score, may underestimate the CV risk in RA, and RA-specific calculators like EULAR multiplier and expanded CV risk prediction score (ERS-RA) do not appear to perform better than the general risk calculators [193,194]. The Reynolds risk score is the only measure that includes CRP, and it may be sensitive to the fluctuating inflammation seen in patients with RA [195]. The addition of CRP to the Framingham risk score and QRISK algorithms was not associated with significant improvement in reclassification of CV risk [196]. There is controversy about which risk calculator to use as the rates of CV events in people with RA are decreasing, but so are those of the matched population, so a gap still exists with more CV events in RA [197,198].

Effects of treatment for RA on CRP levels

Treatment of RA with DMARDs aims to reduce systemic inflammation and improve disease activity. As a measure of systemic inflammation, it would be expected that CRP levels will fall in response to treatment and indeed this is observed during treatment with the different DMARD classes as shown in Supplementary Table 1. Corticosteroids and csDMARDs lead to small decreases in CRP levels [80,199–205]. TNFis decrease CRP levels, generally slightly more than csDMARDs in equivalent patient populations [41,206–209]. JAK inhibitors that target downstream signalling pathways of IL-6 and other cytokines decrease CRP levels by about 10 mg/L, with the reduction tending to be dose dependent [205,209–211]. Overall, the
most rapid, largest, and sustained decreases in CRP levels occur in response to treatment with IL-6R inhibitors, generally resulting in normalization of CRP levels [60,200,201,207,212,213]. Given the predominant role of IL-6 in stimulating CRP production, these results are not surprising.

Consistent with the decreases in CRP levels resulting from IL-6 inhibition, improvements in clinical outcome measures that include CRP have been reported. Indeed, clinical trials have demonstrated that treatment with sarilumab (MOBILITY, MONARCH, and TARGET) results in improvements in DAS28-CRP scores (up to 2.8-point decreases) and higher rates of DAS28-CRP LDA and remission (using standard thresholds of <3.2 [33–49%] and <2.6 [25–34%]) and of ACR20/50/70 response [61–72%/40–46%/16–25%] compared with placebo or, in MONARCH, with adalimumab [60,200,206]. Similar levels have also been seen with tocilizumab in the BREVACTA and SUMMACTA studies [204,214]. Higher rates of SDAI remission with tocilizumab than with TNFi treatment have also been seen in a real-world observational study (SDAI <3.3 32% versus 22%, p < 0.05 at Week 52) [207]. The JAK inhibitor upadacitinib demonstrated superiority to adalimumab for DAS28-CRP LDA and remission in a phase III trial of patients with RA and an inadequate response to methotrexate [215]. Importantly, RA drugs that influence CRP levels have also been shown to improve RA disease activity using scores that do not include a CRP component, indicating their effects on disease activity in RA extend beyond those driven by systemic inflammation. For example, in the most recent sarilumab phase III trial (MONARCH), the primary efficacy endpoint was change in DAS28-ESR at 24 weeks, and sarilumab produced significantly greater improvement than adalimumab (−3.28 versus −2.20, respectively; p < 0.0001) [206].

Subgroup analyses of IL-6R inhibitor RCTs are suggestive of how clinical outcomes may be associated with CRP. Evaluation of baseline CRP subgroups in MOBILITY and MONARCH showed that the treatment effect of sarilumab was greater in the group with baseline CRP >15 mg/L both for radiographic progression (mean modified total Sharp score change at Week 52, sarilumab 0.90–1.00 versus placebo 4.25) [216] and for greater improvement versus adalimumab even when using the DAS28-ESR score [217]. In MOBILITY, patients receiving sarilumab who achieved DAS28-CRP <3.2 versus those who did not exhibited a slightly greater percentage decrease from baseline in CRP after 24 weeks (−97% versus −90%, nominal p < 0.01) [218]. Similar trends were seen in TARGET for ACR50 responders versus non-responders [201]. However, despite the link between IL-6 inhibition and CRP levels, CRP does not appear to be a consistent predictive biomarker for response to tocilizumab treatment. An analysis of BREVACTA and SUMMACTA demonstrated that baseline CRP levels were not predictive of clinical outcomes after tocilizumab treatment [213]. In contrast, the RADIATE study demonstrated that tocilizumab treatment led to a significant decrease in a matrix metalloproteinase-degraded fragment of CRP, reducing tissue inflammation, with the decrease correlating with improvements in pain, functional status, DAS28, and the likelihood of ACR20/50 response [219]. Overall, further investigation of the relationship of baseline and change in CRP levels with clinical outcomes after IL-6 inhibition is needed to understand how they are linked.

There is extremely limited evidence on whether changes in CRP levels resulting from DMARD treatment may also affect the risk for developing or exacerbating comorbidities. In a single-centre longitudinal cohort study of 90 patients with RA who were receiving DMARDs and experienced reductions of CRP >10 mg/L, increases in low-density lipoprotein cholesterol levels and improvements in HDL-C efflux capacity suggested that reducing systemic inflammation improved the lipid profile and potentially reduced CV risk [115]. However, the relationship between reducing CRP levels and a potential reduction in CV risk remains to be elucidated. More research is needed to investigate specific associations between reductions in CRP levels resulting from DMARD treatment and the impact on comorbidities.

In conclusion, CRP is a valuable marker and regulator of systemic inflammation in RA that also appears to play a direct role in bone destruction and radiographic progression. CRP has also been implicated in the aetiology of common comorbidities associated with RA. Reducing CRP levels with RA treatment may contribute to reductions in disease activity, although beneficial effects of RA treatment seem to occur irrespective of CRP values.

Contributions

The authors contributed equally to researching data for the article, substantial discussion of content and writing, reviewing and editing the manuscript before submission.

Declaration of Competing Interest

J.P. reports Grant/research support from AbbVie, BMS, Merck, Pfizer, Roche, UCB, and Seattle Genetics; Consultant for AbbVie, Amgen, Boehringer Ingelheim, BMS, Gilead, Janssen, Lilly, Medexus, Merck, Novartis, Pfizer, Roche, Sanofi, Sandzol, Teva, and UCB.

E.C. reports Grant/research support from Amgen, Bio-Cancer, Chugai Pharma, Ferring Pharmaceuticals, Novimmune, Pfizer, Roche, and UCB; Consultant for AbbVie, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chelsea Therapeutics, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Ferring Pharmaceuticals, Gilead, GlaxoSmithKline, Hospira, Ionis, Janssen, Jazz Pharmaceuticals, MedImmune, Merck Sharp & Dohme, Merrimack Pharmaceuticals, Napp, Novartis, Novimmune, ObSEva, Pfizer, R-Pharm, Regeneron Pharmaceuticals, Inc., Roche, SynAct Pharma, Sanofi Genzyme, Tonix, and UCB; member of speakers bureau for Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharma, Eli Lilly, Hospira, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Sanofi-Aventis, and UCB.

Role of the funding source

The authors received no payment or other compensation for developing this paper. Medical writing support, under the sole direction of the authors, was provided by Gregory Bezkorovainy (Adelphi Communications, Ltd, Macclesfield, UK) and was funded by Sanofi Genzyme, Cambridge MA in accordance with Good Publications Practices (GPP3).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2020.11.005.

References


Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35–45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. *J Rheumatol* 2009;36:1387–90. doi: 10.3899/jrheum.08.10270.


Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35–45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. *J Rheumatol* 2009;36:1387–90. doi: 10.3899/jrheum.08.10270.


