

Soluble CD163 as a Non-Invasive Biomarker in Autoimmune Nephrological and Rheumatological Diseases

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Abstract

Autoimmune nephrological and rheumatological diseases involve macrophage-driven inflammation, yet disease activity is often assessed using invasive or non-specific measures. Soluble CD163 (sCD163), released from activated monocytes and macrophages, is emerging as a biomarker of macrophage-mediated inflammation in these conditions. This narrative review summarizes current evidence on the diagnostic, prognostic, and disease-monitoring potential of sCD163 measured in blood, urine, and synovial fluid in autoimmune nephrological and rheumatological diseases. This review is based on a narrative analysis of selected publications investigating the clinical utility of sCD163 in autoimmune kidney and rheumatic diseases, with emphasis on correlations with disease activity, histopathological findings, and clinical outcomes. Urinary sCD163 shows excellent diagnostic accuracy for active lupus nephritis (area under the receiver operating characteristic [AUROC] 0.89–0.998), correlates with histological activity index (but not chronicity), and distinguishes ongoing inflammation from chronic damage during treatment. In IgA nephropathy, it predicts remission failure and greater benefit from corticosteroids. In ANCA-associated vasculitis, it identifies active renal involvement (AUROC 0.95 in multicenter cohorts). In rheumatoid arthritis (RA), serum sCD163 correlates with early disease activity, predicts radiographic progression, and detects subclinical macrophage activation in remission. In spondylarthritis, synovial fluid sCD163 reflects a disease-specific M2-polarized macrophage phenotype distinct from RA. Utility is compartmentalized: urinary levels indicate intrarenal macrophage activation, synovial fluid local joint inflammation, and serum systemic activation. sCD163 is a promising macrophage-specific biomarker across autoimmune diseases, but its compartmentalized nature requires context-specific measurement. Before clinical implementation, assay standardization, multicenter validation, and interventional trials showing the benefit of sCD163-guided management are needed.

Keywords

sCD163 • Macrophages • Lupus nephritis • IgA nephropathy • ANCA-associated vasculitis rheumatoid arthritis • Spondylarthritis

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Abbreviations

STAT3 – Signal Transducer and Activator of Transcription 3; NF-κB – Nuclear Factor kappa-light-chain-enhancer of activated B cells; PPARγ – Peroxisome Proliferator-Activated Receptor Gamma; HIF-1α – Hypoxia-Inducible Factor 1-alpha; NADPH – Nicotinamide Adenine Dinucleotide Phosphate; ADAM17 – A Disintegrin And Metalloproteinase 17; NIH – National Institutes of Health; SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; MEST-C – Mesangial hypercellularity, Endocapillary hypercellularity, Segmental sclerosis, Tubular atrophy/interstitial fibrosis, Crescents; MCP-1 – Monocyte Chemoattractant Protein-1; TESTING – Therapeutic Evaluation of Steroids in IgA Nephropathy Global; OR – Odds Ratio; HR – Hazard Ratio; CI – Confidence Interval; mRNA – messenger RNA;

ELISA – Enzyme-Linked Immunosorbent Assay; NEPTUNE – Nephrotic Syndrome Study Network; TIMP – Tissue Inhibitor of Metalloproteinases; OPERA – OPTimized treatment algorithm in Early Rheumatoid Arthritis; HOMA-IR – Homeostatic Model Assessment of Insulin Resistance; HMGB1 – High Mobility Group Box 1; MAS – Macrophage Activation Syndrome; TGFBR2 – Transforming Growth Factor Beta Receptor 2; MMP-3 – Matrix MetalloProteinase-3; sTNFR2 – soluble Tumor Necrosis Factor Receptor 2; NGAL – Neutrophil Gelatinase-Associated Lipocalin; STAT3 – Signal Transducer and Activator of Transcription 3; JAK2 – Janus Kinase 2; J-MARINE – Japanese Biomarkers in Nephrotic Syndrome.

1. Introduction

1.1. Role of macrophages in the pathogenesis of autoimmune diseases

Macrophages play a central role in immune responses and are key contributors to the pathogenesis of autoimmune and inflammatory diseases. Depending on microenvironmental signals, macrophages can acquire distinct functional phenotypes, classically described as pro-inflammatory (M1) or alternatively activated (M2) (Mills et al. 2000; Mantovani et al. 2004). Macrophages exhibit remarkable plasticity, existing

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primarily as pro-inflammatory M1 or anti-inflammatory M2 phenotypes (Mantovani et al. 2004; Chen et al. 2023). M1 macrophages (classically activated) are typically induced by factors like lipopolysaccharide (LPS) and interferon (IFN)- γ , and they express surface markers such as CD80, CD86, and inducible nitric oxide synthase (iNOS) while secreting pro-inflammatory cytokines like tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6 to assist in host defense. M1 macrophages promote inflammation through the production of pro-inflammatory cytokines, reactive oxygen species (ROS), and enhanced antigen presentation. Conversely, M2 macrophages (alternatively activated) are induced by IL-4 or IL-13 and express markers like CD206 (mannose receptor), CD163, and Arginase-1 (Arg-1) (Chen et al. 2023). M2 macrophages are primarily involved in immune regulation, tissue remodeling, and fibrotic processes and play vital roles in tissue repair, wound healing, and angiogenesis, even though they can also be “educated” by tumor cells to promote immune escape and metastasis. In fact, macrophage polarization is a dynamic process, and the M1 and M2 phenotypes represent only the extremes of a broad spectrum of activation states. The M2 macrophage population is particularly heterogeneous and is divided into four main subtypes with distinct functions and stimulating factors:

M2a: induced by IL-4 or IL-13; responsible for wound healing and fibrosis through the secretion of transforming growth factor (TGF)- β , insulin-like growth factor, and fibronectin.

M2b: activated by immune complexes and Toll-like receptor agonists; characterized by high IL-10 production, performing strong immunomodulatory and anti-inflammatory functions.

M2c: induced by IL-10, TGF- β , or glucocorticoids; crucial for phagocytosis of dead cells, immunosuppression, and tissue remodeling.

M2d: activated, among others, by IL-6 and adenosine A2 receptor agonists; promotes angiogenesis and tumor metastasis (through vascular endothelial growth factor secretion) (Strizova et al. 2023).

Key Signaling Mechanisms and Transcription Factors involved in macrophage polarization are:

- **STAT3:** Serves as a central hub in the signaling network, generally promoting the M2 phenotype. It integrates signals from the JAK/STAT pathway and crosstalks with others like PI3K/AKT, Notch, Hedgehog, and Wnt (Wingless-related integration site).
- **NF- κ B:** Traditionally viewed as a “master switch” for M1 pro-inflammatory responses, though its inhibition can sometimes promote M2 polarization depending on the context.

- **PPAR γ :** This nuclear receptor controls macrophage skewing by promoting the M2 phenotype and inhibiting M1 activation, often acting through the regulation of lipid metabolism.
- **HIF-1 α :** Essential for the activation of inflammatory M1 macrophages, particularly by driving glycolytic M1/M2 balance is disrupted (Chen et al. 2023; Xia et al. 2023).

Metabolic shifts are fundamental to macrophage fate decisions. M1 macrophages rely heavily on anaerobic glycolysis and the pentose phosphate pathway, which generates NADPH for ROS production and pathogen killing. They also feature a “broken” Tricarboxylic Acid Cycle — the Krebs cycle (TCA) that leads to the accumulation of citrate and succinate, the latter of which stabilizes HIF-1 α to promote inflammation further. In contrast, M2 macrophages depend on oxidative phosphorylation and fatty acid oxidation to meet the energy demands for long-term tissue remodeling. Arginine metabolism is a defining difference: M1 cells use iNOS to produce nitric oxide, whereas M2 cells use Arg-1 to produce ornithine and proline, which are precursors for collagen synthesis and tissue repair (Yadav et al. 2022).

Although this dichotomous classification represents an oversimplification of macrophage biology, it remains a useful framework for understanding macrophage heterogeneity in chronic immune-mediated diseases (Gordon and Martinez 2010; Sica and Mantovani 2012; Murray et al. 2014).

In autoimmune conditions, dysregulated macrophage activation contributes both to sustained inflammation and to progressive tissue damage. Activated macrophages infiltrate affected tissues, amplify local immune responses, and interact with cells of the adaptive immune system, thereby perpetuating autoimmune responses. In glomerulonephritis, macrophage accumulation — particularly in the tubulointerstitium — correlates with the degree of renal dysfunction and predicts disease progression (Nikolic-Paterson and Atkins 2001). In rheumatoid arthritis (RA), macrophages are among the most abundant cell types in the inflamed synovium, and their activation products critically contribute to both inflammation and irreversible cartilage destruction (Kinne et al. 2007). In parallel, macrophages exhibiting alternatively activated phenotypes have been implicated in chronic tissue remodeling and fibrosis — processes that are particularly relevant in organ-specific autoimmune diseases. Experimental and clinical evidence indicates that macrophage-driven pathways link immune activation with subsequent structural tissue damage, positioning macrophages at the interface between inflammation and long-term organ dysfunction (Wynn and Vannella 2016).

Macrophages are also an important source of disease-relevant biomarkers. Proteins selectively expressed or released by activated macrophages may reflect ongoing immune processes within affected tissues and provide insight into disease activity and progression. Conventional inflammatory markers such as

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), although widely used, are produced primarily by hepatocytes in response to IL-6 and reflect systemic inflammation in a non-specific manner (Pepys and Hirschfield 2003). They do not capture macrophage-driven processes at the tissue level. Therefore, biomarkers that originate directly from activated macrophages — such as sCD163 — may offer a more specific window into key immunopathological mechanisms in autoimmune diseases (Møller 2012).

1.2. CD163 as a marker of macrophage activation: receptor biology

CD163 is a macrophage-specific scavenger receptor predominantly expressed on cells of the monocyte–macrophage lineage. It is preferentially associated with alternatively activated macrophages and is considered a hallmark of macrophage responses involved in immune regulation and resolution of inflammation. Functionally, CD163 serves as the hemoglobin–haptoglobin (Hb:Hp) scavenger receptor, mediating the clearance of hemoglobin complexes and thereby contributing to protection against oxidative stress and tissue injury (Kristiansen et al. 2001; Gordon and Martinez 2010). Inflammatory milieu dynamically regulates expression of CD163. Anti-inflammatory mediators, including IL-10 and glucocorticoids, upregulate CD163 expression, whereas pro-inflammatory stimuli such as TNF- α and IFN- γ downregulate surface expression. This regulation links immune activation with resolution and reflects macrophage functional states rather than simple cell presence (Møller 2012; Etzerodt and Moestrup 2013).

CD163 expression is not restricted to a single disease context but has been described across a wide spectrum of inflammatory and immune-mediated conditions. In autoimmune diseases, increased CD163 expression is observed in tissues characterized by chronic inflammation, macrophage infiltration, and ongoing tissue remodeling, supporting the concept that CD163 reflects macrophage involvement in disease-relevant immunopathological processes (Etzerodt and Moestrup 2013; Wynn and Vannella 2016).

These biological properties support the investigation of CD163 as a disease-relevant biomarker. Its macrophage specificity and regulated expression in response to immune signals make it a suitable candidate for monitoring macrophage-driven processes in autoimmune nephrological and rheumatological diseases.

1.3. sCD163: shedding mechanisms and clinical relevance

sCD163 represents the circulating form of the CD163 receptor and arises through proteolytic cleavage of the membrane-bound molecule. This process, commonly referred to as

shedding, is primarily mediated by the metalloproteinase ADAM17 (also known as tumor necrosis factor- α -converting enzyme, TACE). Shedding occurs in response to macrophage activation and inflammatory stimuli, resulting in release of sCD163 into extracellular fluids. This mechanism links sCD163 directly to macrophage activation, providing a biological basis for its use as a marker of macrophage-driven immune processes (sf).

Increased levels of sCD163 reflect functional changes in macrophage activity rather than simple macrophage abundance. In healthy individuals, serum sCD163 concentrations range from approximately 1–4 mg/L (Møller 2012; Etzerodt and Moestrup 2013). Unlike conventional inflammatory markers produced by hepatocytes, sCD163 originates directly from activated macrophages and therefore provides more specific insight into macrophage-related immune pathways. Since shedding of CD163 is a direct response to inflammatory triggers, sCD163 is used as a potent biomarker for macrophage activation in various diseases. Although CD163 is an M2 marker, its “solubilization” or shedding is paradoxically linked to pro-inflammatory (M1-like) stimuli, making it a unique bridge between these two phenotypes. High levels of sCD163 are often associated with systemic inflammation, sepsis, and macrophage-related disorders where the delicate M1/M2 balance is disrupted (Yadav et al. 2022; Chen et al. 2023; Møller 2012; Etzerodt and Moestrup 2013). sCD163 can be measured in serum or plasma, reflecting systemic macrophage activation, as well as in compartment-specific fluids such as urine or synovial fluid. The presence of sCD163 in these fluids allows assessment of local macrophage-driven inflammation in organ-specific disease settings. This property is particularly relevant for immune-mediated diseases in which tissue inflammation may not be adequately captured by systemic biomarkers alone.

Despite these advantages, interpretation of sCD163 levels requires consideration of biological context. sCD163 is not disease-specific and may be elevated across a range of inflammatory and immune-mediated conditions. However, its specificity lies at the cellular level, as sCD163 reflects activation of CD163-expressing macrophages rather than non-specific systemic inflammation. Therefore, its clinical utility depends on interpretation within specific disease contexts and use of standardized analytical approaches (Møller 2012; Etzerodt and Moestrup 2013).

1.3.1. The complexity of “soluble CD163”

The term sCD163 refers to the presence of this receptor in biological fluids (such as plasma), and as noted in your query, it exists in two distinct forms. While the provided sources focus on membrane-bound CD163, the following details on its soluble forms are derived from broader scientific consensus (not explicitly detailed in the sources):

- **Ectodomain Shedding (Proteolytic Cleavage):** Under inflammatory conditions, the membrane-bound CD163 ectodomain is rapidly cleaved. This process is mediated by the metalloproteinase ADAM17 (also known as TACE, or TNF- α converting enzyme). This shedding is often triggered by pro-inflammatory stimuli such as LPS, which classically drives M1 polarization.
- **Extracellular Vesicle (EV) Association:** In addition to the cleaved protein, CD163 can be found in a non-cleaved form attached to the membranes of EVs or exosomes. The sources confirm that macrophages, particularly under stress or in the tumor microenvironment (TME), actively secrete exosomes that carry immunoregulatory proteins and can influence the polarization of neighboring cells (Chen et al. 2023; Plevriti et al. 2024; Tan et al. 2026).

1.4. The need for non-invasive biomarkers in nephrology and rheumatology

Despite significant advances in understanding the immunopathogenesis of autoimmune diseases, clinical assessment of disease activity in both nephrology and rheumatology still relies largely on tools that are either invasive or insufficiently specific. In nephrology, renal biopsy remains the gold standard for diagnosing and classifying glomerulonephritis, grading histological activity and chronicity, and guiding therapeutic decisions. Yet biopsy is inherently limited as a monitoring tool — it carries procedural risks, captures only a snapshot of a dynamic process, and cannot be repeated at the frequency required for meaningful longitudinal follow-up. Clinicians therefore depend on surrogate parameters such as proteinuria, serum creatinine, and estimated glomerular filtration rate, none of which directly reflect the type or intensity of 63 adaptive changes, such as proteinuria. In lupus nephritis (LN), conventional laboratory parameters do not reliably reflect the degree of histological activity, and clinical remission does not always correspond to resolution of intrarenal inflammation (Malvar et al. 2017). Moreover, in the case of proteinuria, the use of urinary sCD163 (usCD163) normalized to urinary protein can improve the clinical ability to distinguish renal vasculitis flare from flare mimics in ANCA-associated vasculitis (AAV) (Moran et al. 2021).

In rheumatology, the situation is similarly imperfect. Composite disease activity indices integrate clinical and laboratory data but ultimately depend on markers such as CRP and ESR, which measure systemic inflammation without distinguishing the cellular source. Imaging studies in RA have shown that subclinical synovitis is detectable in a substantial proportion of patients classified as being in clinical remission (Brown et al. 2006). This discrepancy underscores the need for biomarkers that capture key immunopathological mechanisms rather than non-specific inflammatory responses.

What is lacking across both disciplines is a biomarker that is non-invasive, easily measurable in routine biological fluids, reflective of a specific and disease-relevant immune pathway, and suitable for serial monitoring. Markers derived from the effector cells that drive tissue damage — rather than downstream, non-specific acute-phase reactants — would represent a fundamental improvement. Given the central role of macrophage activation in both glomerulonephritis and systemic rheumatic diseases, soluble products of macrophage origin are particularly attractive candidates in this regard.

2. Aim

The study aimed to evaluate the usefulness of sCD163 as a non-invasive biomarker in the diagnosis and monitoring of autoimmune diseases of nephrological and rheumatological origin based on current literature data.

3. Search Strategy

The study was conducted as a narrative review. Articles available in the MEDLINE/PubMed and Embase databases were analyzed. The search strategy was divided into two separate parts.

The first part focused on nephrological diseases in which macrophage infiltration is a recognized pathological feature, including IgA nephropathy (IgAN), membranous nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, LN, and AAV.

The second part covered selected rheumatic diseases in which sCD163 may act as a biomarker: RA, polymyalgia rheumatica (PMR), fibromyalgia, and spondylarthritis (SpA), with particular emphasis on psoriatic arthritis (PsA).

For each disease entity, we examine whether sCD163 — measured in serum, plasma, urine, or synovial fluid — has demonstrated value for diagnosis, assessment of disease activity, prediction of histopathological findings, monitoring of treatment response, or prognostication. We also identify methodological limitations of the existing studies and highlight areas where further research is needed.

To the best of our knowledge, no previous review has addressed the role of sCD163 across both nephrological and rheumatological autoimmune conditions within a single work. By bringing together evidence from these two closely related yet often separately studied fields, we aim to provide a broader perspective on the clinical potential and current limitations of this macrophage-specific biomarker.

The analysis covered publications from the last 20 years. Particular emphasis was placed on large observational studies and research of significant importance for routine clinical practice.

Due to the nature of a narrative review, the study does not constitute a complete synthesis of all available literature.

Rather, the study aimed to identify current challenges and potential directions for the development of the use of the sCD163 biomarker in research and clinical practice, taking into account its current limitations.

4. sCD163 in Autoimmune Nephrological Diseases

4.1. Lupus nephritis (LN)

Lupus nephritis is the disease in which usCD163 has been studied most extensively. The biological rationale is straightforward: CD163 is expressed on M2 macrophages that infiltrate inflamed glomeruli, and its soluble form is shed into the urine following inflammatory activation. Endo et al. (2016) showed that usCD163 levels correlated with the number of CD163-positive macrophages in glomerular tissue from LN biopsies, directly linking the urinary signal to intrarenal macrophage infiltration. Zhang et al. (2020) extended this observation by interrogating publicly available single-cell RNA sequencing data from 24 LN kidneys (originally reported by Arazi et al. 2019). They found that M2 macrophages were the predominant CD163-expressing cell type in the renal infiltrate — a notable finding given that M1 macrophages are generally considered dominant in systemic lupus erythematosus (SLE). The authors suggested that this discrepancy indicates that the intrarenal immune environment may differ substantially from the peripheral blood compartment.

Several groups have evaluated the diagnostic performance of usCD163 for identifying active LN, and the results have been remarkably consistent. Mejia-Vilet et al. (2020) measured usCD163 in two independent cohorts (Mexican, $n = 120$; Ohio, $n = 129$) and reported an area under the receiver operating characteristic (AUROC) of 0.998 and 0.980, with a cutoff of >130 ng/mmoL providing 97% sensitivity and 94% specificity. Zhang et al. (2020) confirmed the elevation of usCD163 in active LN across three ethnic groups (African-American, Caucasian, and Asian) from centers in Baltimore, Hong Kong, and Dallas (all $p < 0.001$). Gupta et al. (2021) reported similar findings in 122 Indian SLE patients, where usCD163 outperformed anti-dsDNA antibodies, C3, and C4 in identifying active nephritis. Huang et al. (2022) demonstrated in 261 Taiwanese SLE patients that usCD163 correlated with renal SLEDAI, proteinuria, anti-dsDNA levels, and chronic kidney disease stage. Of note, Mejia-Vilet et al. (2020) found no correlation between plasma and usCD163, indicating that the urinary signal reflects local macrophage activity within the kidney rather than filtration of circulating protein.

Beyond diagnostic accuracy, usCD163 appears to reflect the type and severity of histological lesions. Zhang et al. (2020) analyzed 45 LN patients with matched urine and biopsy specimens and found usCD163 to be significantly higher in proliferative

LN (class III/IV) than in non-proliferative forms (class II/V; $p < 0.001$). The AUC for this distinction was 0.89 — higher than for C3 (0.70), C4 (0.52), anti-dsDNA (0.54), or urine protein-to-creatinine ratio (0.70). usCD163 correlated with the activity index and its individual components — fibrinoid necrosis, cellular crescents, and interstitial inflammation — but showed no correlation with the chronicity index. This distinction is clinically relevant: a marker that tracks active inflammation without reflecting chronic scarring could help guide decisions about intensifying or de-escalating immunosuppressive therapy. Mejia-Vilet et al. (2020) observed a concordant pattern, with usCD163 correlating with the NIH activity index ($r = 0.48$ – 0.59) but not with the chronicity index. They also noted that usCD163 was unaffected by corticosteroid dose, addressing the concern that immunosuppressive treatment might confound the biomarker.

Overall, reported AUROCs range from 0.89 in biopsy-matched analyses (Zhang et al. 2020) to above 0.97 in larger validation cohorts (Mejia-Vilet et al. 2020; Renaudineau et al. 2024). In all studies, usCD163 outperformed traditional serological markers, though the degree of this advantage depended on the comparator population and the clinical question being addressed.

Longitudinal data add a further dimension to these findings. Gupta et al. (2021) followed patients over 12 months and observed that usCD163 declined progressively with treatment. In several patients who relapsed, usCD163 rose before clinical parameters worsened, indicating the possibility that this marker could detect subclinical reactivation of glomerular inflammation before it becomes clinically apparent.

Perhaps the most clinically compelling data come from the repeat biopsy analysis by Mejia-Vilet et al. (2020). The authors used two different cutoff values to address two different clinical questions. The lower cutoff (>130 ng/mmoL) was designed to identify active LN at diagnosis — a screening question where high sensitivity is essential. The higher cutoff (>370 ng/mmoL) addressed a more difficult clinical problem encountered during follow-up: when a patient still has proteinuria after 6 months of treatment, is this because inflammation is ongoing, or because the kidney has sustained irreversible damage? This distinction matters because the two scenarios call for opposite management strategies — escalation of therapy in the first case, acceptance of residual damage in the second. In 19 patients who underwent repeat biopsies, usCD163 above or below 370 ng/mmoL agreed perfectly ($\kappa = 1.0$) with a histologic activity index above or below 1. At 6 months, usCD163 below 370 ng/mmoL predicted complete renal response at 12 months with $>87\%$ sensitivity and specificity. Renaudineau et al. (2024) provided further support for this approach, reporting that changes in usCD163 over time could predict impending flares and remissions.

Serum sCD163 has been studied separately, and the picture is somewhat different. Yang et al. (2021) measured serum

sCD163 in 121 biopsy-proven LN patients and found that it correlated with both the activity and chronicity indices, as well as with serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate. Patients with elevated serum sCD163 had worse renal survival at a mean follow-up of 25 months (85.71% vs. 94.44%; $p = 0.017$). The authors suggested that serum sCD163, unlike its urinary counterpart, may capture a broader dimension of disease — not just glomerular inflammation but also systemic macrophage activation and cumulative renal damage. In a different clinical context, Nishino et al. (2019) showed that serum sCD163 could help identify SLE-associated macrophage activation syndrome (86% specificity), and noted that it appears to play a different role from serum ferritin in this setting.

There are, however, important limitations to this body of evidence. Most studies are single-center and cross-sectional, with moderate sample sizes. Assay platforms vary between laboratories, urinary concentrations are reported in different units (pg/mg vs. ng/mmol creatinine), and proposed cutoff values cannot be directly compared across studies (Endo et al. 2016; Gupta et al. 2021; Huang et al. 2022). No prospective trial has yet tested whether treatment guided by usCD163 measurements actually improves patient outcomes.

The ongoing J-MARINE study (Kurasawa et al. 2024), a nationwide Japanese cohort enrolling 365 patients with glomerular diseases across 61 centers — including 51 with LN — should help address some of these gaps. It is the largest prospective effort to date to validate usCD163 in a standardized setting, and its results will be relevant both for assay harmonization and for evaluating whether usCD163 works best alone or as part of a composite biomarker panel.

4.2. IgA nephropathy

In IgAN, macrophage infiltration follows a different pattern than in LN. Gong et al. (2021) measured usCD163 in 349 patients with biopsy-confirmed IgAN and found that it correlated with tubulointerstitial CD163-positive macrophage infiltration but not with glomerular CD163-positive macrophages. This observation is consistent with the known predominance of tubulointerstitial injury in IgAN and contrasts with LN, where the glomerular compartment is primarily affected. usCD163 also correlated with disease severity across all Oxford Classification parameters (all $p \leq 0.0002$), and patients in the highest usCD163 tertile had a 2.66-fold greater risk of remission failure at 6 months. A composite model combining usCD163 with clinical variables and MEST-C scores yielded the best predictive performance (AUC 0.788); notably, adding IL-6 or MCP-1 did not improve the model, suggesting that usCD163 provides prognostic information related to macrophage activity that other inflammatory markers do not capture.

Li et al. (2024) extended these findings using data from 517 patients with IgAN and, critically, from the Chinese participants of the TESTING randomized controlled trial. In the cross-sectional cohort, usCD163 correlated with CD163-positive macrophage infiltration in glomeruli, crescentic lesions, and the tubulointerstitium, and was strongly associated with active histological lesions, particularly endocapillary hypercellularity and crescents. In the TESTING trial, patients with baseline usCD163 above the median derived substantially greater benefit from corticosteroid therapy in terms of proteinuria remission at 6 months (OR 35.56 vs. 3.94 for those below the median; p for interaction = 0.036). Both full-dose and reduced-dose methylprednisolone significantly lowered usCD163, and a 50% or greater reduction from baseline was independently associated with a lower risk of kidney progression events (adjusted HR 0.52; 95% CI 0.30–0.93). These results position usCD163 as a potential tool for guiding immunosuppressive treatment decisions in IgAN.

4.3. AAV

Monitoring renal disease activity in AAV is particularly challenging. As Moran et al. (2021) noted, up to 70% of AAV patients develop renal involvement, and an estimated 43% of those who progress to end-stage kidney disease do so without a clinically detected flare. This means that in a substantial proportion of patients, conventional monitoring tools fail to capture ongoing renal damage.

O'Reilly et al. (2016) found that CD163 mRNA was markedly upregulated in glomeruli from ANCA-associated glomerulonephritis compared with controls. In a study of 479 individuals including patients with small vessel vasculitis, disease controls, and healthy controls, usCD163 identified active renal vasculitis with 83% sensitivity and 96% specificity.

The most comprehensive clinical validation was performed by Moran et al. (2021), who tested a diagnostic-grade ELISA across four independent cohorts. In a prospective cohort of 84 patients with suspected renal flare, the AUROC was 0.95, with a negative predictive value of 95.2% among those assessed as possible flares. The authors stressed that usCD163 could be particularly useful for ruling out active renal vasculitis without resorting to biopsy — a procedure that carries risks and is not always feasible. They proposed a clinical cutoff of 250 ng/mmol based on the 97.5th centile in healthy controls. Villacorta et al. (2020) independently confirmed these findings in a cohort of 47 AAV patients, of whom 24 were prospectively followed from diagnosis and 23 served as remission controls. A 20% increase in usCD163 from the preceding measurement detected relapse with 100% sensitivity and 89% specificity, and usCD163 concentrations correlated with Birmingham Vasculitis Activity Scores during follow-up.

4.4. Other glomerulopathies

For other glomerular diseases, the evidence is limited and comes mainly from disease-control arms of the studies discussed above. O'Reilly et al. (2016) detected CD163 mRNA in microdissected glomeruli from patients with diabetic nephropathy and nephrotic syndrome, but at markedly lower levels than in small vessel vasculitis. Mejia-Vilet et al. (2020) similarly reported lower usCD163 in focal segmental glomerulosclerosis and membranous nephropathy compared with active LN. Nielsen et al. (2020) established a laboratory reference interval for usCD163 based on 253 healthy individuals and reported an AUROC of 0.97 for distinguishing glomerulonephritis from controls; notably, the usCD163-to-albumin ratio was higher in proliferative than in non-proliferative forms of glomerulonephritis, suggesting that this normalization approach may help distinguish macrophage-driven inflammation from non-specific protein leak. Prospective studies systematically comparing usCD163 across different types of glomerulonephritis are still lacking.

One methodological observation from Moran et al. (2021) deserves particular attention. In 65 patients with primary podocytopathies from the NEPTUNE program, usCD163 was elevated during nephrotic syndrome even though there was no macrophage infiltration — the sCD163 was leaking through the damaged glomerular barrier from the circulation. The authors showed that normalizing usCD163 to total urine protein instead of creatinine corrected this artifact. This has practical implications wherever usCD163 is measured in patients with heavy proteinuria, and it is worth keeping in mind when interpreting results in settings where nephrotic-range proteinuria may coexist with glomerular inflammation.

5. sCD163 in Autoimmune Rheumatological Diseases

5.1. RA

Macrophages are among the most abundant immune cells in the rheumatoid synovium, and their number correlates with disease activity and radiographic progression. Because CD163 is expressed exclusively on cells of the monocyte–macrophage lineage, sCD163 provides a specific readout of macrophage activation in RA.

Matsushita et al. (2002) were the first to measure sCD163 systematically in RA. In a cohort of 49 patients with established disease, serum sCD163 was significantly elevated compared with 18 healthy controls ($p < 0.0001$) and correlated weakly with CRP ($r = 0.29$, $p < 0.05$). Synovial fluid concentrations were consistently higher than in matched serum — in one patient up to 22-fold — pointing to substantial local production by activated synovial macrophages. The

study also showed that TIMP-3, but not TIMP-1 or TIMP-2, inhibited CD163 shedding, implicating a member of the ADAMs family rather than classical matrix metalloproteinases as the responsible sheddase.

Greisen et al. (2011) extended these findings longitudinally in 34 patients with early RA (disease duration less than 6 months). Notably, baseline plasma sCD163 was not significantly higher than in healthy volunteers (median 1.69 vs. 1.66 mg/L), yet it correlated with DAS28 ($r = 0.464$; $p = 0.0057$), CRP, and ESR. After 9 months of treatment, sCD163 decreased significantly ($p = 0.001$), and the post-treatment level predicted radiographic progression over 5 years ($r = 0.468$, $p = 0.018$), whereas DAS28 did not. In a larger subsequent study using the OPERA trial cohort, the same group reported baseline sCD163 of 2.39 mg/L in early RA vs. 1.63 mg/L in healthy controls ($p < 0.001$), with a 23.5% decrease after 3 months of treatment (Greisen et al. 2015). sCD163 levels rose significantly following withdrawal of adalimumab at 12 months despite clinically stable disease on methotrexate (1.72–2.10 mg/L, $p = 0.0001$), suggesting that sCD163 captures subclinical macrophage activation not reflected by composite disease activity indices.

The relationship between sCD163 and disease activity appears to differ in established RA. Jude et al. (2013) measured sCD163 in 33 patients with long-standing RA (mean 7.2 years) and found it significantly elevated ($p = 0.0001$), with 59% of patients above the normal cut-off. sCD163 showed weak positive associations with CRP ($r = 0.51$) and rheumatoid factor ($r = 0.48$) but did not correlate with DAS28 or clinical manifestations. In contrast, sCD163 correlated strongly with IL-12 ($r = 0.99$) and CXCL10 ($r = 0.99$), suggesting that in long-standing disease it reflects chronic macrophage–lymphocyte crosstalk rather than acute disease activity.

At the tissue level, Fonseca et al. (2002) showed that CD163 was expressed on virtually all CD14-positive cells in RA synovium but was reduced in areas rich in CD4-positive IFN- γ -producing T lymphocytes. This is consistent with the known downregulation of CD163 by IFN- γ and suggests that circulating sCD163 represents a composite signal from CD163-low (T cell-rich, M1-polarized) and CD163-high (T cell-poor, M2-polarized) microenvironments within the same joint.

Taken together, sCD163 in RA correlates with disease activity in early disease and predicts long-term radiographic progression, even when baseline levels do not differ significantly from healthy controls. It responds to treatment but rises again after biologic withdrawal. In established RA, sCD163 remains elevated but appears to decouple from DAS28. This dissociation between sCD163 and clinical measures suggests potential utility in monitoring subclinical macrophage activation during treatment de-escalation.

5.2. SpA

Spondyloarthropathies, which include PsA, exhibit a characteristic synovial macrophage phenotype that distinguishes them from RA and are therefore discussed separately.

The landmark study by Baeten et al. (2004) compared synovial biopsies from 26 SpA and 23 RA patients and found that CD163-positive macrophages, but not CD68-positive macrophages, were significantly increased in SpA vs. RA. This difference was more pronounced in HLA-B27-positive patients. Local sCD163 production was substantial: synovial fluid levels were five- to seven-fold higher than in matched serum and correlated with lining layer CD163-positive macrophages. In contrast, serum sCD163 was only moderately elevated, did not correlate with synovial fluid levels or inflammatory parameters, and was unaffected by infliximab. These findings indicate that sCD163 in SpA reflects local synovial macrophage activation rather than systemic inflammation — a fundamentally different compartmentalization pattern from RA. An additional finding was an inverse correlation between CD163 expression and lymphocyte activation (CD69-positive cells), suggesting that CD163-positive macrophages in SpA actively suppress adaptive immune responses.

Vandooren et al. (2009) substantiated this picture by analyzing synovial fluid cytokines in 47 SpA (including 15 PsA), 55 RA, and 14 other arthritis patients. SpA synovial fluid showed significantly lower levels of M1-derived mediators (TNF α , IL-1 β , IL-12p70) compared with RA, while macrophages expressed increased CD163 and CD200R. When SpA synovial fluid was used to condition monocytes *in vitro*, it promoted differentiation toward a CD163-positive/CD200R-positive phenotype. Critically, PsA patients displayed cytokine and macrophage profiles indistinguishable from non-psoriatic SpA, supporting a common macrophage-mediated pathogenic mechanism across the SpA spectrum.

Ambarus et al. (2012) refined these observations by examining synovial sublayers separately in 18 SpA and 20 RA patients. The increased CD163 expression in SpA was restricted to the intimal lining layer, where macrophages co-expressed CD163 and CD32, consistent with an IL-10-polarized phenotype. Sublining macrophages showed no differences between diseases and co-expressed both M1 and M2 markers. These findings indicate that the M2-like phenotype in SpA is shaped by local cytokine gradients at the synovial surface rather than a systemic predisposition.

In axial SpA, Heftdal et al. (2018) found that serum sCD163 was within the normal range but decreased slightly during anti-TNF- α treatment, while sCD206 (another M2 marker) increased. This divergent pattern suggests that the two markers reflect different macrophage subtypes or activation states, and that the macrophage biology in axial disease may differ from peripheral SpA.

Finally, Arias de la Rosa et al. (2022) linked sCD163 to the broader systemic inflammatory burden in PsA. In 100 PsA patients compared with 100 healthy controls, sCD163 was elevated and associated with insulin resistance (AUC 0.730 for HOMA-IR >3.07), higher disease activity, and poorer treatment response. The authors identified two cardio-metabolic phenotypes through cluster analysis. Apremilast reduced sCD163, body mass index, and HOMA-IR in the high-risk cluster, while methotrexate monotherapy was metabolically ineffective, positioning sCD163 as a potential marker bridging joint inflammation and cardiovascular comorbidity.

5.3. Systemic juvenile idiopathic arthritis

Systemic juvenile idiopathic arthritis (sJIA) is a severe auto-inflammatory disease in which monocytes and macrophages serve as key effector cells. CD163, a scavenger receptor expressed exclusively on cells of the monocyte-macrophage lineage, plays an important anti-inflammatory role by binding and clearing Hb:Hp complexes and HMGB1-haptoglobin complexes. Ligand engagement of CD163 triggers the production of IL-10 and heme oxygenase-1, thereby limiting tissue damage and promoting resolution of inflammation (Do et al. 2018).

In children with active sJIA, increased surface expression of CD163 on circulating monocytes and markedly elevated serum levels of sCD163 are observed. Levels are particularly high during MAS, both in tissue macrophages and in the soluble form. Although CD163 expression is strongly induced by IL-10 (characteristic of the M (IL-10) or former M2c phenotype), monocytes in sJIA display a mixed phenotype combining features of M (IL-10) and M (LPS + immune complex) polarization.

Do et al. (2018) elegantly demonstrated that two microRNAs upregulated in active sJIA — miR-125a-5p and miR-181c — regulate CD163 expression through distinct mechanisms. miR-181c directly targets the 3'UTR of CD163 mRNA, leading to its degradation. In contrast, miR-125a-5p acts indirectly by suppressing the α -subunit of the IL-10 receptor (IL10RA) and TGFBR2, thereby impairing IL-10 signaling and downstream CD163 induction. Both miRNAs are preferentially induced under M (LPS + IC) conditions, creating a negative feedback loop that counteracts the autocrine anti-inflammatory effects of IL-10 in this mixed macrophage phenotype.

Functionally, overexpression of miR-181c significantly impairs the macrophages' ability to produce IL-10 in response to Hb:Hp and HMGB1:Hp complexes, thereby attenuating CD163-dependent anti-inflammatory functions. In MAS, this regulatory network appears to be disrupted, resulting in further upregulation of CD163, possibly due to IFN- γ -mediated suppression of the inhibitory microRNAs.

These findings highlight the complex, finely tuned regulation of CD163 in sJIA and suggest that sCD163 may serve not only as a biomarker of disease activity and MAS but also as a functional indicator of altered macrophage polarization and defective resolution of inflammation.

5.4. PMR and fibromyalgia

Evidence on sCD163 in PMR is limited and comes indirectly from the giant cell arteritis (GCA) literature, as the two conditions share a macrophage-driven pathogenic continuum. Gloor et al. (2018) prospectively measured immune-inflammatory biomarkers in 14 GCA patients treated with tocilizumab plus glucocorticoids in the first phase 2 randomized controlled trial of tocilizumab in GCA. Serum sCD163 was suppressed below healthy control levels during the early stages of combined therapy and gradually increased toward normal levels by week 52 under tocilizumab monotherapy ($p = 0.0012$). The authors interpreted the early suppression as a profound anti-inflammatory effect of combined immunosuppression, and the subsequent normalization as reconstitution of macrophage homeostasis. Other markers (MMP-3, pentraxin-3, sTNFR2) remained elevated despite clinical remission, documenting subclinical disease activity that was most

pronounced during early treatment. These findings suggest that at least 52 weeks of IL-6 pathway inhibition may be needed to reset inflammatory mechanisms. While potentially relevant to PMR, where subclinical vasculitis is increasingly recognized, dedicated studies in isolated PMR cohorts are lacking.

To the best of our knowledge, no studies have measured sCD163 in fibromyalgia, consistent with its non-inflammatory, central sensitization-driven pathophysiology. Because fibromyalgia frequently coexists with RA and SpA and complicates disease activity assessment, future studies could explore whether sCD163 serves as a negative discriminator between inflammatory and non-inflammatory musculoskeletal pain. Nevertheless, taken together, although the evidence base for sCD163 in rheumatological diseases is less extensive and robust than in nephrological conditions, available data consistently indicate its association with macrophage activation. In RA and SpA, sCD163 reflects disease activity and subclinical inflammation, while in sJIA it shows particular promise as a biomarker of disease activity and MAS. Further studies are needed to establish its clinical utility in routine rheumatological practice.

Table 1 summarizes the key clinical applications and observations of CD163 across autoimmune nephrological and rheumatic diseases.

Table 1. Overview of clinical applications and key observations of CD163 in autoimmune nephrological and rheumatic diseases (Jude et al. 2013; Zhang et al. 2020; Gong et al. 2021; Moran et al. 2021)

Disease	Biomarker	Key clinical application	Key observations	Statistical significance
LN	usCD163	Diagnosis of active LN, assessment of response to treatment	Correlation with activity index (not chronicity), decrease after treatment	AUROC 0.89–0.998
IgAN	usCD163	Stratification of the risk of events related to kidney disease progression	It correlates with the infiltration of CD163-positive macrophages in the tubulointerstitium, but not in the glomeruli	AUROC 0.788
AAV	usCD163	Diagnosis of active renal vasculitis, ruling out active disease without biopsy	High negative predictive value	AUROC 0.95
RA	sCD163	Monitoring disease activity in early RA, predicting the progression of radiological changes, potential significance in dose tapering	Correlation with DAS8 in early RA, no correlation in LSRA	Strong correlation with IL-12 and CXCL ($r = 0.99$, both) in LSRA
SpA	sCD163	Reflects local synovial macrophage activation rather than systemic inflammation	M2-like phenotype in SpA is shaped by local cytokine gradients at the synovial surface	N/A (mainly qualitative/quantitative observations)
PMR	sCD163	Monitoring subclinical disease activity during treatment (indirectly from GCA studies)	At least 52 weeks of IL-6 pathway inhibition may be needed to reset inflammatory mechanisms	N/A (data mainly from GCA, no studies in isolated PMR)
Fibromyalgia	Missing	Potential negative discriminator	Negative discriminator between inflammatory and non-inflammatory musculoskeletal pain	Hypothesis for future research

AAV, ANCA-associated vasculitis; AUROC, area under the receiver operating characteristic; GCA, giant cell arteritis; IgAN, IgA nephropathy; IL, interleukin; LN, lupus nephritis; LSRA, long-standing rheumatoid arthritis; PMR, polymyalgia rheumatic; RA, rheumatoid arthritis; sCD163, soluble CD163; SpA, spondyloarthritis; usCD163, urinary soluble CD163.

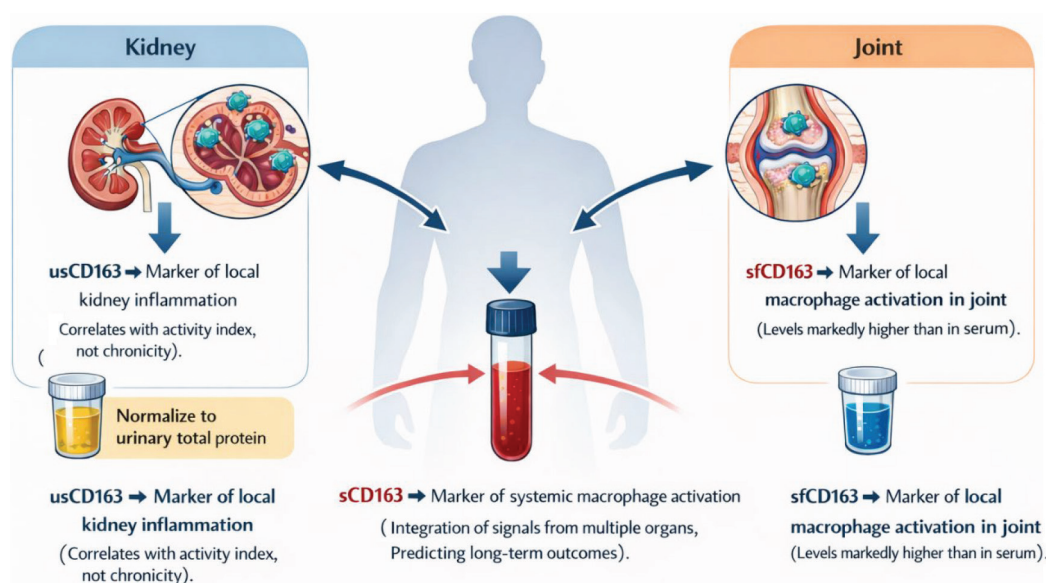


Fig 1. Compartmentalization of clinical information carried by sCD163 in kidney and joint diseases (Matsushita et al. 2002; Baeten et al. 2004; Etzerodt and Moestrup 2013; Mejia-Vilet et al. 2020; Zhang et al. 2020). sCD163, soluble CD163; usCD163, urinary soluble CD163; sfCD163: synovial fluid sCD163.

6. Comparison Across Biological Fluids

A distinguishing feature of sCD163 as a biomarker is its compartmentalization: the same molecule carries different clinical information depending on the biological fluid in which it is measured. This property reflects the fact that sCD163 is produced locally by activated macrophages within inflamed tissues and is not simply a systemic acute-phase reactant (Figure 1).

In the kidney, usCD163 appears to originate predominantly from intrarenal macrophages rather than from filtration of circulating protein. Mejia-Vilet et al. (2020) demonstrated no correlation between plasma and usCD163 (Pearson $r = 0.04$), and Zhang et al. (2020) confirmed through single-cell transcriptomic analysis that CD163-expressing M2 macrophages are the principal source within inflamed glomeruli. Accordingly, usCD163 correlates with the histological activity index but not with the chronicity index in LN, whereas serum sCD163 correlates with both indices and with renal survival (Yang et al. 2021). This distinction has practical implications: usCD163 appears better suited for detecting active inflammation amenable to immunosuppressive treatment, while serum sCD163 may capture a broader dimension of disease that includes cumulative organ damage. One important caveat is that in patients with heavy proteinuria, sCD163 may leak through the damaged glomerular barrier from the circulation, producing falsely elevated urinary levels unrelated to local macrophage activity. Moran et al. (2021) showed that normalizing usCD163 to total urine protein rather than creatinine corrects this artifact — a methodological consideration

relevant whenever usCD163 is measured in the context of nephrotic-range proteinuria.

In the joint, synovial fluid sCD163 (sfCD163) concentrations consistently exceed matched serum levels by a substantial margin. Matsushita et al. (2002) reported up to 22-fold higher levels in synovial fluid than in serum in individual RA patients, and Baeten et al. (2004) found five- to seven-fold elevations in SpA. These gradients confirm local production by activated synovial macrophages. In SpA, sfCD163 correlated with lining layer CD163-positive macrophages, whereas serum sCD163 did not correlate with synovial fluid levels, inflammatory parameters, or treatment response to infliximab (Baeten et al. 2004). This dissociation indicates that serum sCD163 in SpA is a poor surrogate for local synovial macrophage activation — a fundamentally different pattern from early RA, where serum sCD163 correlates with disease activity indices.

Serum or plasma sCD163 provides a systemic readout that integrates macrophage activation across multiple tissue compartments. In early RA, plasma sCD163 correlates with DAS28 and predicts radiographic progression (Greisen et al. 2011, 2015). In long-standing RA, the correlation with disease activity is lost while associations with IL-12 and CXCL10 emerge, suggesting a shift toward chronic macrophage–lymphocyte interactions (Jude et al. 2013). In GCA, serum sCD163 responds to immunosuppressive treatment and tracks subclinical disease activity not captured by CRP (Gloor et al. 2018). In PsA, elevated serum sCD163 associates with insulin resistance and cardiometabolic risk, extending its potential relevance beyond joint inflammation (Arias de la Rosa et al. 2022).

Taken together, these observations indicate that sCD163 is a compartmentalized biomarker whose clinical utility depends on matching the measurement site to the clinical question. usCD163 is most informative for renal inflammation, sfCD163 for joint-specific macrophage activation, and serum sCD163 for systemic macrophage-driven processes and long-term prognostication. This compartmentalization is both a strength — enabling tailored assessment of organ-specific pathology — and a limitation, as no single measurement captures the full spectrum of macrophage involvement across disease manifestations.

7. Discussion

The evidence reviewed here supports the concept that sCD163 is a clinically informative biomarker of macrophage activation in autoimmune nephrological and rheumatological diseases. Several consistent findings emerge across diseases and study designs. First, sCD163 levels are elevated in active disease compared with healthy controls and with inactive disease in virtually all conditions examined. Second, sCD163 correlates with histopathological markers of macrophage-driven inflammation — glomerular macrophage infiltration in LN and IgAN, synovial lining macrophages in SpA. Third, sCD163 responds to immunosuppressive treatment, declining with effective therapy and rising with disease reactivation or biologic withdrawal.

The strongest evidence exists for usCD163 in LN, where multiple independent cohorts have reported AUROCs exceeding 0.90 for identifying active nephritis, and where the repeat biopsy data from Mejía-Vilet et al. (2020) provide compelling evidence that usCD163 can distinguish ongoing inflammation from chronic damage during follow-up. In AAV, the diagnostic-grade ELISA validation by Moran et al. (2021) across four cohorts represents the most advanced stage of biomarker development in this field. In IgAN, Li et al. (2024) provided the first evidence from a randomized controlled trial that usCD163 can identify patients who derive greater benefit from immunosuppressive therapy — a critical step toward biomarker-guided treatment. In rheumatology, the data are more heterogeneous but suggest that sCD163 captures aspects of macrophage biology not reflected by conventional composite indices, particularly subclinical activation during apparent remission.

Several methodological limitations must be acknowledged. Most studies are single-center and cross-sectional, with sample sizes typically ranging from 30 to 350 patients. Assay platforms differ between laboratories: some use commercially available ELISAs, others employ in-house assays, and urinary concentrations are reported in different units (pg/mg creatinine, ng/mmol creatinine, or absolute concentrations), making direct comparison of cutoff values across studies difficult. The influence of confounders such as concurrent infections, obesity, and hepatic disease — all of which can elevate sCD163 — has not been systematically addressed.

Furthermore, no study has yet demonstrated that treatment decisions guided by sCD163 measurements improve clinical outcomes compared with standard care.

A comparison between the nephrological and rheumatological settings reveals important differences in the maturity of the evidence. In nephrology, the availability of biopsy-matched data has enabled direct correlation between usCD163 and tissue-level macrophage infiltration, providing a strong biological anchor for the biomarker signal. The clinical question is also well defined: clinicians need a non-invasive tool to determine whether persistent proteinuria reflects active inflammation or irreversible damage. In rheumatology, the situation is more complex. Synovial biopsy is not part of routine clinical practice in most settings, and the clinical questions are more diffuse — ranging from early diagnosis to monitoring treatment de-escalation to predicting radiographic progression. Consequently, the role of sCD163 in rheumatology is less clearly delineated, although its ability to detect subclinical macrophage activation during clinical remission represents a potentially valuable niche.

The macrophage phenotype associated with sCD163 also differs between diseases. In SpA and PsA, sCD163 reflects a predominantly M2-polarized, IL-10-driven synovial environment that is fundamentally distinct from the M1-dominated milieu of RA. This has implications for interpretation: elevated sCD163 in SpA may indicate an anti-inflammatory macrophage program, whereas in RA and LN it is more likely to reflect macrophage turnover and inflammatory shedding mediated by ADAM17. Future studies should consider these disease-specific contexts when interpreting sCD163 levels.

Looking forward, several developments could advance this field. The ongoing J-MARINE study (Kurasawa et al. 2024) should provide standardized, multicenter prospective data on usCD163 across glomerular diseases. Assay harmonization and the establishment of internationally agreed reference intervals are prerequisites for clinical implementation. Studies exploring composite panels that combine sCD163 with complementary biomarkers — such as MCP-1, NGAL, or calprotectin — may improve diagnostic accuracy and prognostic power beyond what sCD163 achieves alone. Finally, and most importantly, interventional trials that use sCD163 measurements to guide therapeutic decisions are needed to move this biomarker from research to clinical practice.

7.1. Therapeutic modulation strategies

The recognition of macrophage plasticity and the central role of M2-like macrophages in sustaining chronic inflammation and tissue remodeling opens the door to therapeutic reprogramming strategies. Although sCD163 itself is not a direct therapeutic target, its levels can serve as a dynamic, non-invasive pharmacodynamic biomarker to monitor the efficacy of macrophage-directed therapies.

TME: Strategies focus on converting M2-like tumor-associated macrophages (TAMs) into M1 anti-tumor macrophages. This can be achieved by altering the TME's acidity with proton scavengers like CaCO₃ or using chloroquine to increase lysosomal pH.

Nanotechnology: Nanocarriers such as mannosylated liposomes or gold/silver nanoparticles are used to deliver immunomodulators directly to macrophages to reset their polarization state.

Targeting Signaling and Metabolism: Pharmacological targeting of STAT3 or JAK2 (e.g., using cucurbitacin B) can suppress M2-mediated tumor metastasis. Similarly, metabolic inhibitors like 2-Deoxy-D-Glucose, which blocks glycolysis, or CB-839, which inhibits glutaminase, can be used to reprogram macrophages in inflammatory or malignant conditions.

Disease-Specific Applications: In chronic conditions like Sjogren's syndrome, M2 macrophages have been identified as key players in nerve damage and vasculitis, suggesting they could be specific targets for treating peripheral neuropathy. Shifting the M1/M2 balance is also being explored for atherosclerosis, obesity-induced insulin resistance, and RA.

8. Conclusions

sCD163 is a macrophage-specific biomarker that provides clinically relevant information in autoimmune nephrological and rheumatological diseases. In LN, usCD163 offers excellent diagnostic accuracy for active nephritis, correlates with histological activity, and can distinguish ongoing inflammation from chronic damage during treatment follow-up. In IgAN, it predicts treatment response to corticosteroids. In AAV, it identifies active renal involvement with high sensitivity and specificity and may reduce the need for repeat biopsies. In RA, it captures subclinical macrophage activation not reflected by composite disease activity indices. In SpA, it reflects a disease-specific M2-polarized synovial macrophage phenotype.

The clinical utility of sCD163 is inherently compartmentalized: usCD163 informs about renal macrophage activation, sfCD163 about joint-specific processes, and serum sCD163 about systemic macrophage-driven inflammation and long-term prognosis. This compartmentalization requires clinicians to match the measurement site to the clinical question.

Key gaps remain. Assay standardization, prospective multicenter validation, and — most critically — interventional trials demonstrating that sCD163-guided management improves patient outcomes are needed before this biomarker can be incorporated into routine clinical practice. The convergence of evidence from both nephrology and rheumatology supports continued investment in this macrophage-specific marker as a tool for personalized assessment of autoimmune disease activity.

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AI Use

Artificial intelligence–assisted tools were used solely for technical support in preparing a conceptual figure, strictly based on detailed instructions provided by the authors. No AI tools were used to generate scientific content, interpret data, or formulate conclusions.

Authors' Contributions

Dorota Kamińska: Conceptualization, literature review, writing — original draft preparation, writing — review and editing; Paweł Poznański: Literature review, writing — original draft preparation; Wojciech Tański: Literature review, writing — original draft preparation; Anna Skotny: Conceptualization, writing — review and editing, supervision. All authors contributed to the interpretation of the literature, critically revised the manuscript for important intellectual content, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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