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Dramatic Reduction of Complement System Factors in Rheumatoid Arthritis Patients Treated with Tocilizumab †

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† Dedicated to the memory of Prof. Roberto Perricone.

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Abstract: Background. Rheumatoid arthritis (RA) is a chronic autoimmune disease driven by inflammatory pathways involving cytokines and complement activation. Interleukin-6 (IL-6) promotes hepatic synthesis of acute-phase proteins, including complement components C3 and C4. Tocilizumab (TCZ), a humanized monoclonal antibody targeting the IL-6 receptor, has proven effective in RA management. However, its impact on the complement system remains poorly characterized. **Methods and Results**. We studied 10 patients with moderate-to-severe RA treated with intravenous TCZ (8 mg/kg/month) over 48 weeks. Serum levels of C3, C4, CH50, ESR, and CRP were assessed at baseline and at 4, 12, 24, 36, and 48 weeks. Complement activation was monitored via C3 and factor B split products. A rapid and sustained reduction in C3 and C4 levels was observed starting at week 4, without changes in CH50 or detectable cleavage products. This reduction coincided with significant improvement in inflammatory markers and clinical outcomes (DAS28 and HAQ scores). **Conclusions**. IL-6R blockade with TCZ is associated with a rapid and sustained reduction in complement proteins C3 and C4. In a proportion of patients, complement levels reached values below the lower limit of normal during follow-up, while CH50 remained stable and complement split products were not detected. These findings are consistent with altered acute-phase/hepatic regulation of complement under IL-6 inhibition rather than overt complement consumption. The clinical significance of complement reduction and its role as a biomarker of treatment response require confirmation in larger studies.

Keywords: rheumatoid arthritis; IL-6; tocilizumab; complement; C3; C4

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease primarily characterized by persistent synovial inflammation leading to progressive joint destruction, functional disability, and increased morbidity. While its precise etiology remains elusive, immune dysregulation and chronic inflammation driven by a network of cytokines, autoantibodies, and innate immune effectors have been recognized as central to its pathogenesis. Among these, the complement system has garnered increasing attention for its role in perpetuating synovial inflammation. As a key component of innate immunity, the complement cascade is traditionally known for its role in host defense; however, it also contributes to tissue damage and chronic inflammation in autoimmune diseases [1]. In RA, immune complexes formed within the synovium can activate the classical complement pathway, resulting in the generation of pro-inflammatory split products and membrane attack complexes that amplify joint inflammation and damage [2]. Interleukin-6 (IL-6) is a multifunctional cytokine with a pivotal role in the inflammatory milieu of RA. It orchestrates a variety of biological activities including B-cell maturation, T-cell activation, osteoclastogenesis, and hepatic acute-phase protein production. Given its central role, IL-6 has emerged

as a crucial therapeutic target. Tocilizumab (TCZ), a humanized monoclonal antibody against the IL-6 receptor (IL-6R), has shown robust efficacy in clinical trials and real-world studies by damping systemic inflammation and improving clinical outcomes in RA patients [3]. Importantly, IL-6 is also a major inducer of hepatic synthesis of acute-phase proteins, including certain complement components such as C3 and C4 [4]. This suggests a regulatory loop wherein IL-6 drives complement protein synthesis, potentially augmenting inflammatory damage in RA. Despite this plausible interaction, limited data exists on how IL-6 blockade influences systemic complement profiles in RA patients, others are available in systemic lupus erythematosus [5–8]. In this study, we aimed to explore the effects of IL-6R inhibition by TCZ on circulating complement components in a cohort of RA patients with active disease. We hypothesized that IL-6 blockade may not only suppress traditional markers of inflammation such as ESR and CRP but also reduce complement protein levels, reflecting a potential anti-inflammatory mechanism beyond direct immunosuppression. Understanding these dynamics could provide insights into novel biomarkers for disease activity and response to therapy and unveil new therapeutic avenues in the management of RA.

2. Methods and Results

We investigated the serum complement profile in 10 patients (1 M, 9 F, age 67 ± 12 years old, disease duration 72 ± 8 months) suffering from moderate to severe RA diagnosed according to ACR/EULAR 2010 revised criteria (mean DAS28 at baseline 6151 ± 1141, mean HAQ at baseline 1.87 ± 0.8) and its modifications during treatment with the IL-6R antagonist TCZ. Patients' consents were acquired. Ethical approval was obtained. All procedures were conducted in accordance with the Declaration of Helsinki. Patients enrolled were unresponsive to or had contraindications for conventional DMARDs. They were treated with intravenous TCZ as monotherapy at the dosage of 8 mg/Kg/month. Plasma levels of C3, C4, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and CH50 were evaluated at baseline, and after 4, 12, 24, 36 and 48 weeks of treatment. The complement system activation was evaluated at each time through dosage of split products of C3 and factor B in patients' sera.

Before initiating Tocilizumab, the mean complement C3 level in the patient cohort under investigation was 114 mg/dL ± 17 mg/dL. As shown in Figure 1, there was a significant reduction in circulating C3 levels already at 4 weeks and up to 48 weeks of treatment compared to baseline. No patients had low C3 at baseline versus 7/10 (70%) at 48 weeks. C4 levels at T0 were on average 24 mg/dL ± 7.47 mg/dL and consistently decreased at different time points. No patients had low C4 at baseline versus 5/10 (50%) at 48 weeks. No significant changes in CH50 were observed during therapy compared to baseline levels. Moreover, complement cleavage products were not detected. The lowest recorded values were C3 67 mg/dL and C4 10 mg/dL (Table 1).

Table 1. Clinical and laboratory parameters a baseline and at 48 weeks.

Clinical and Laboratory Parameters	T0 Baseline		T48 Weeks		*p* Value
	Mean	Std. Deviation	Mean	Std. Deviation	
Age (years)	66.7	12.14			
disease duration (years)	12.4	8.631			
ESR (mm/h)	52.7	31.61	28.22	29.8	0.08
CRP (mg/dL)	7.563	8.625	0.4867	0.8989	0.032
Rheumatoid factor (U/L)	32.66	43.52	43.47	72.55	ns
aCCP (U/L)	200.5	189.7	279.9	290.4	ns
ANA	60%		30%		
anti-DNA (U/L)	83.82	241.3	93.93	270.6	ns
ACLA GPL	6.09	6.675	7.574	12.67	ns
ACLA MPL	4.749	4.234	6.332	6.604	ns
LAC	0	0	0	0	
C3 (mg/dL)	113.9	17.02	97.33	28.01	0.049
C4 (mg/dL)	24.38	7.474	19.34	11.68	0.045
CH50	113.4	24.93	105.5	21.61	ns
C1INH (mg/dL)	31.42	6.088	25.59	6.703	0.047
HB g/L	12.09	1.628	12.38	1.694	ns
PLT	269.2	70.48	241	54.54	ns
GB	7.709	2.636	6.12	2.053	ns
N%	65.7	8.619	61.18	8.69	ns
L%	24.95	7.638	28.21	8.759	ns
M%	7.228	2.68	7.71	3.281	ns
TNF	17.32	13.9	20.31	20.17	ns
TJC	13.29	9.304	6.667	2.066	ns

Table 1. *Cont.*

Clinical and Laboratory Parameters	T0 Baseline		T48 Weeks		*p* Value
	Mean	Std. Deviation	Mean	Std. Deviation	
SJC	6.857	4.67	2.333	3.83	ns
GH	43.33	32.04	53.33	20.66	ns
PtGH	70	19.15	51.67	23.17	ns
DAS28-ESR	6.151	1.141	4.093	1.877	ns
HAQ	1.857	0.7976	1.6	0.6782	ns
Lymphocytes/mcl	1786	569	1557	465.1	ns
CD3 %	80.9	6.262	81	6.864	ns
CD3 n	1445	469.7	1250	360.4	ns
CD4 %	56.3	10.57	56.3	11.64	ns
CD4 n	997.2	330.9	857.7	339.6	ns
CD8 %	25.1	10.9	24.9	12.94	ns
CD8 n	453.2	260	367.9	202.2	ns
CD19 %	5	3.367	5.4	4.142	ns
CD19 n	94.5	85.3	91.7	89.49	ns
NK %	13.4	3.688	13.3	5.165	ns
NK n	233.2	103.6	214.9	111.7	ns
IgG	1053	408.7	992.3	343.9	ns
IgA	251.8	148.2	235.4	129.7	ns
IgM	110.8	88.47	109.2	89.38	ns
Triglicerides (mg/dL)	91.5	21.82	118.6	61.16	ns
Tot. Cholesterol (mg/dL)	209	29.85	236.4	50.77	ns
LDL (mg/dL)	122.4	21.03	135.8	28.54	ns
HDL (mg/dL)	66.7	13.82	64.2	13.89	ns

No significant difference in C3 and C4 levels was documented between FR or anti-CCP positive and negative patients before and during treatment. Disease activity and inflammatory markers decreased markedly during treatment compared to baseline values (although not significantly due to small sample size). C3 levels correlated with Spearman's test, Figure 2). Low disease activity was achieved in 4 patients and remission in 2 patients (Table 1).

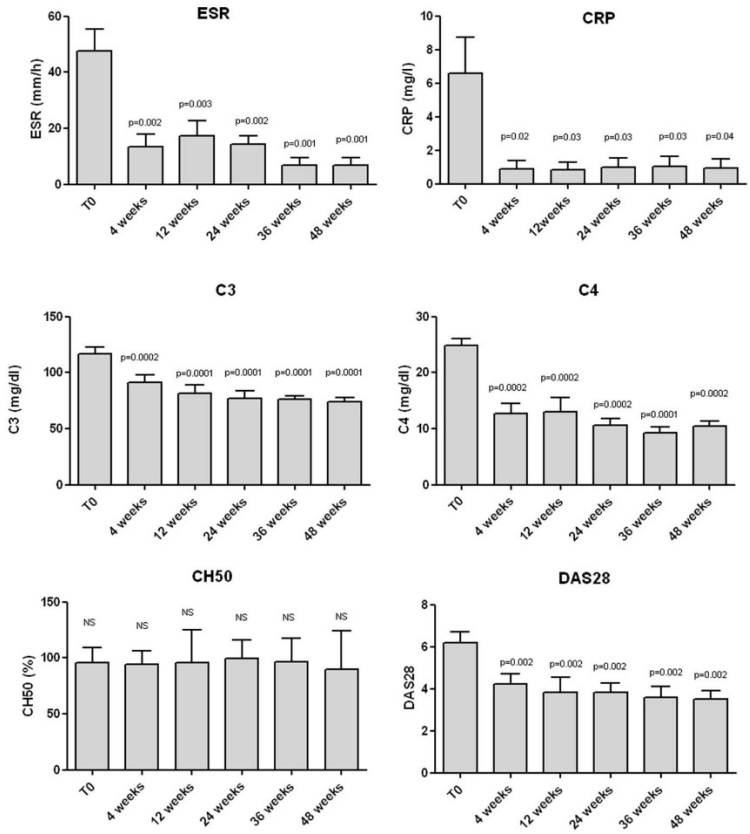

Figure 1. Modification of clinical and laboratory parameters during 48 weeks of observation.

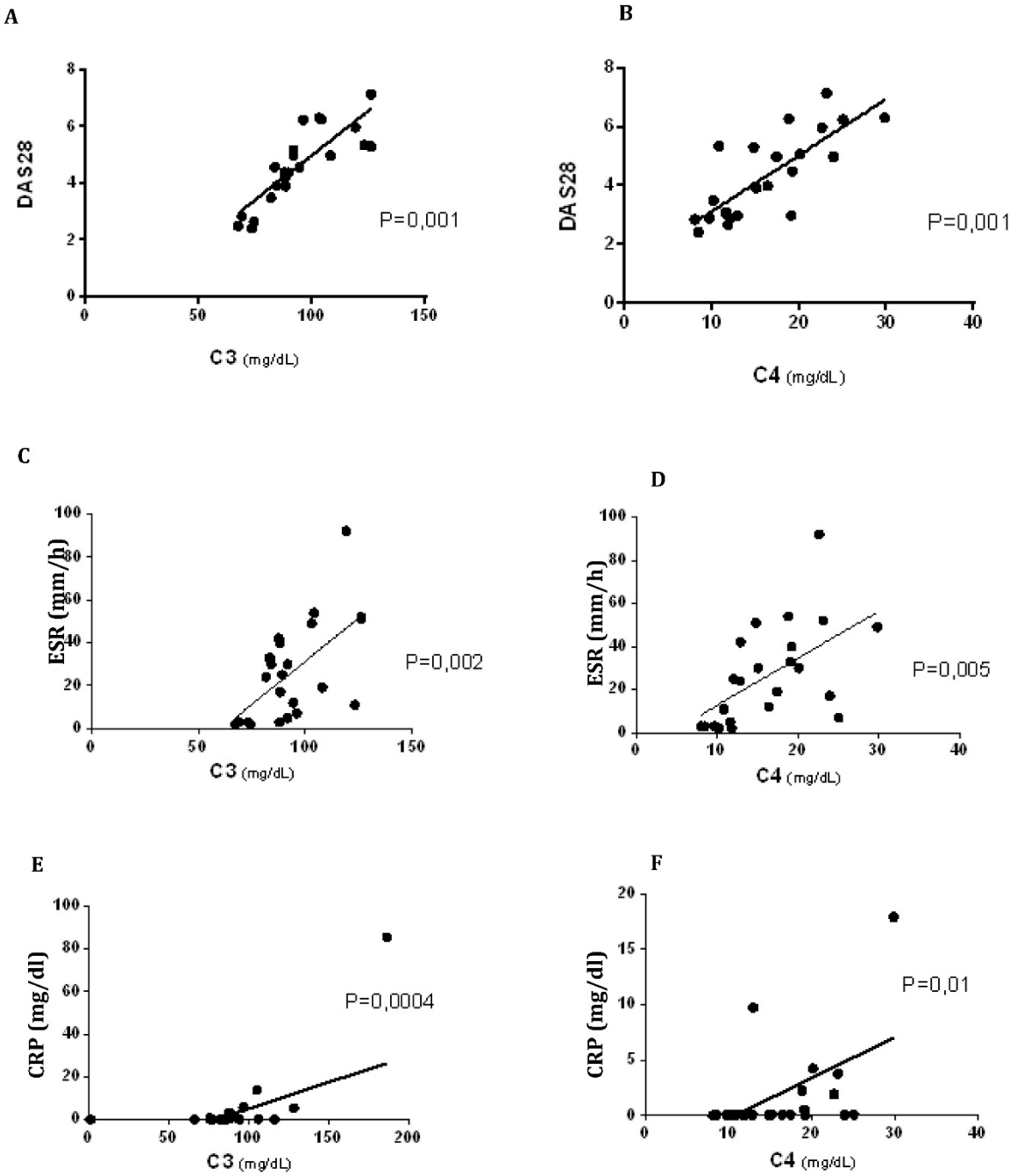

Figure 2. Correlation between serum C3 and C4 levels and disease activity and inflammatory markers in patients treated with tocilizumab. Serum C3 and C4 levels were correlated with DAS28 (panels **A** and **B)**, and with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (panels **C**, **D**, and **E** and **F**, respectively).

At 48 weeks DAS28 was 3.50 ± 1.28 demonstrating a moderate response according to EULAR response criteria [5]. Mean HAQ decreased to 1.2 ± 0.70. Based on the EULAR clinical response, patients were divided into non-responders and responders. Changes in C3 and C4 levels were then evaluated in responders and non-responders at 3 months after the start of treatment. It was demonstrated that C3 and C4 levels significantly decreased only in responders ($p = 0.01$ for both comparisons, respectively)

3. Discussion

The findings of our study demonstrate a significant and sustained reduction in the serum levels of complement components C3 and C4 in RA patients undergoing IL-6R blockade with tocilizumab. Notably, this decline was observable as early as four weeks into treatment and paralleled clinical improvements in DAS28 and functional status assessed by HAQ. These results demonstrate that complement proteins are dynamically modulated during IL-6R blockade. However, given the limited sample size and exploratory nature of this study, complement changes should

be interpreted as a pharmacodynamic effect of IL-6 inhibition rather than validated biomarkers of therapeutic response [9,10]. The small sample size precluded stratified analyses according to sex, BMI, or serological subgroups, and limits the ability to draw definitive conclusions regarding mechanisms or clinical utility.

Reduced complement levels in inflammatory diseases may reflect either increased consumption due to immune-complex–mediated activation or reduced hepatic production secondary to modulation of acute-phase pathways. In rheumatoid arthritis, complement activation within inflamed synovium is well documented and typically results in reduced circulating C3 and C4 due to consumption. In our cohort, the absence of detectable complement split products and the stability of CH50 do not support overt systemic complement consumption during TCZ therapy. These findings are consistent with altered acute-phase/hepatic regulation of complement under IL-6 blockade, although localized activation or alternative mechanisms cannot be fully excluded. Importantly, our data do not allow definitive attribution of complement reduction to suppressed synthesis alone [11,12]. By blocking IL-6R, TCZ may interrupt this upstream signal, thereby reducing systemic complement availability. These results are consistent with prior literature indicating the modulation of complement pathways during anti-cytokine therapies in autoimmune diseases [12]. Our study adds to this body of evidence by providing longitudinal data on complement dynamics in patients treated with TCZ [13]. Notably, earlier studies have also suggested that targeting IL-6 or TNF-α can lead to a downregulation of complement synthesis, reinforcing the interplay between cytokine-driven inflammation and innate immune effectors. Clinically, the reduction in complement levels observed in our cohort may have therapeutic relevance. Complement activation contributes not only to inflammation but also to joint erosion and damage via recruitment of neutrophils and generation of anaphylatoxins [14]. Thus, by limiting complement availability, TCZ may exert additional protective effects on joint structures beyond its immunomodulatory action [15].

Recent work by Ferraz-Amaro et al. [7] demonstrated that both classical and alternative complement pathway activity decreases during TCZ therapy, even after adjustment for disease activity. These findings support the concept that IL-6R blockade modulates complement independently of clinical response. Accordingly, complement measurements should not be interpreted as markers of disease activity or treatment efficacy, but rather as indicators of IL-6–driven inflammatory pathway modulation.

Theoretical concerns have been raised regarding infection risk in the setting of hypocomplementemia. In our cohort, despite some patients reaching sub-normal C3 and C4 values, no increase in infectious events was observed. However, this study is not powered to assess safety outcomes, and larger cohorts are required to determine whether complement reduction under TCZ has clinically relevant implications for infection risk [16,17]. However, the absence of significant adverse events related to infections in our cohort suggests that the degree of complement suppression achieved with TCZ is not clinically detrimental in this regard.

Nevertheless, vigilance is warranted in long-term follow-up. From a translational perspective, our findings support the potential utility of complement measurements as biomarkers of IL-6 blockade efficacy. Moreover, they open the door to future studies exploring combination therapies that target both cytokines signaling and complement activation in RA and possibly other autoimmune conditions. In conclusion, IL-6R inhibition via TCZ leads to a pronounced decline in complement proteins C3 and C4, likely reflecting reduced synthesis rather than consumption. From a translational perspective, our findings add to growing evidence that IL-6R blockade exerts measurable effects on the complement system. While these changes reflect IL-6–dependent inflammatory regulation, they should not currently be used to guide clinical decision-making. Future studies integrating complement dynamics with long-term outcomes and safety endpoints are required. This novel observation adds another layer of understanding to the mechanisms by which IL-6 blockade confers therapeutic benefits in RA and may inform the development of future therapeutic strategies targeting the complement pathway.

Author Contributions

C.P.: conceptualization, methodology, writing—original draft preparation, software; L.B. data curation, writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Ethical review and approval were waived for this study, due to retrospective observational design.

Informed Consent Statement

Patient consent was waived due to retrospective observational design.

Data Availability Statement

Data is available upon request to the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest. The authors take full responsibility for the content of the published article. Given the role as Editor-in-Chief, Carlo Perricone had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. Chen, M.; Daha, M.R.; Kallenberg, C.G. The complement system in systemic autoimmune disease. *J. Autoimmun.* **2010**, *34*, J276–J286. https://doi.org/10.1016/j.jaut.2009.11.014.
2. Okroj, M.; Heinegård, D.; Holmdahl, R.; et al. Rheumatoid arthritis and the complement system. *Ann. Med.* **2007**, *39*, 517–530. https://doi.org/10.1080/07853890701477546.
3. Mihara, M.; Kasutani, K.; Okazaki, M.; et al. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R. *Int. Immunopharmacol.* **2005**, *5*, 1731–1740. https://doi.org/10.1016/j.intimp.2005.05.010.
4. Ramadori, G.; Van Damme, J.; Rieder, H.; et al. Interleukin 6 modulates hepatic protein synthesis in human and mouse. *Eur. J. Immunol.* **1988**, *18*, 1259–1264. https://doi.org/10.1002/eji.1830180817.
5. Illei, G.G.; Shirota, Y.; Yarboro, C.H.; et al. Tocilizumab in systemic lupus erythematosus: Data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. *Arthritis Rheum.* **2010**, *62*, 542–552. https://doi.org/10.1002/art.27221.
6. Romano, C.; Del Mastro, A.; Sellitto, A.; et al. Tocilizumab reduces complement C3 and C4 serum levels in rheumatoid arthritis patients. *Clin. Rheumatol.* **2018**, *37*, 1695–1700. https://doi.org/10.1007/s10067-018-3992-7.
7. Ferraz-Amaro, I.; Santos-Concepción, S.; Castro-Hernández, J.; et al. Tocilizumab modulates the activity of the classical and alternative complement pathways in rheumatoid arthritis patients. *Front. Immunol.* **2025**, *16*, 1486588. https://doi.org/10.3389/fimmu.2025.1486588.
8. Bieber, A.; Markovits, D.; Toledano, K.; et al. Hypocomplementemia during tocilizumab treatment: Long-term follow-up results. *Medicine* **2022**, *101*, e29528. https://doi.org/10.1097/MD.0000000000029528.
9. Ballanti, E.; Perricone, C.; Greco, E.; et al. Complement and autoimmunity. *Immunol. Res.* **2013**, *56*, 477–491. https://doi.org/10.1007/s12026-013-8422-y.
10. Di Muzio, G.; Perricone, C.; Ballanti, E.; et al. Complement system and rheumatoid arthritis: Relationships with autoantibodies, serological, clinical features, and anti-TNF treatment. *Int. J. Immunopathol. Pharmacol.* **2011**, *24*, 357–366. https://doi.org/10.1177/039463201102400209.
11. Markiewski, M.M.; Lambris J.D. The role of complement in inflammatory diseases from behind the scenes into the spotlight. *Am. J. Pathol.* **2007**, *171*, 715–727. https://doi.org/10.2353/ajpath.2007.070166.
12. Tanaka, T.; Narazaki, M.; Kishimoto, T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb. Perspect. Biol.* **2014**, *6*, a016295. https://doi.org/10.1101/cshperspect.a016295.
13. Genovese, M.C.; McKay, J.D.; Nasonov, E.L.; et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis. *Arthritis Rheum.* **2008**, *58*, 2968–2980. https://doi.org/10.1002/art.23940.
14. Hashizume, M.; Mihara, M. Blockade of IL-6 and TNF-α inhibited the production of MMP-1 and MMP-3. *Eur. J. Pharmacol.* **2011**, *31*, 493–496. https://doi.org/10.1016/j.ejphar.2012.05.035.
15. Shetty, A.; Hanson, R.; Korsten, P.; et al. Tocilizumab in the treatment of rheumatoid arthritis and beyond. *Drug Des. Dev. Ther.* **2014**, *8*, 349–364. https://doi.org/10.2147/DDDT.S41437.
16. Scott, D.L.; Wolfe, F.; Huizinga, T.W. Rheumatoid arthritis. *Lancet* **2010**, *376*, 1094–1108. https://doi.org/10.1016/S0140-6736(10)60826-4.
17. Smolen, J.S.; Aletaha, D.; McInnes, I.B. Rheumatoid arthritis. *Lancet* **2016**, *388*, 2023–2038. https://doi.org/10.1016/S0140-6736(16)30173-8.