Rheumatoid Arthritis: Understanding the Burden and the Significance of the Interleukin 6 Pathway

This supplement was developed by HMP Communications, LLC, and sponsored by Sanofi and Regeneron.

Rheumatoid arthritis (RA) is a chronic progressive systemic autoimmune disease that is driven by a complex network of cytokines.[1,2] This debilitating disease results in joint damage that leads to disability, impaired quality of life, and premature death.[1,3] RA is marked by inflammation typically impacting the lining of the joints (synovitis), particularly of the hands and feet. Chronic synovial inflammation and hyperplasia attacks the body's tissues triggering cartilage and bone destruction and joint deformity, with affected joints showing pain, swelling, and redness that can lead to prolonged stiffness and compromised physical function.[3-6]

Furthermore, RA is a heterogeneous disease with a complex presentation varying from slowly progressive symptoms to more severe disease associated with nodules and systemic inflammation.[3] Because treatment course is variable among patients, RA is a challenge for clinicians to manage and results in substantial costs.[7]

The exact cause of RA remains unknown; however, it has been demonstrated that the cytokine interleukin 6 (IL-6) can be integral to the pathogenesis of RA.[8] This disease state update provides a brief overview of the disease burden. Additionally, the role of IL-6 and how it mediates its effects through intracellular signaling pathways is discussed, with the aim of providing a better understanding of the molecular mechanisms of the disease.

Burden of RA

RA is estimated to affect 1.5 million adults in the United States and approximately 1% of the Western adult population, with a female to male ratio of 3:1.[3-5] A positive family history of RA increases the risk approximately 3 to 5 times.[9] In a study of the largest registry of RA patients in the United States, Solomon and colleagues found that the majority of patients were women 45 years of age and older.[10]

The etiology of RA is unknown, but genetic and environmental factors are contributory, as well as gender and age-associated factors that play a role in the disease process.[1,5] Recent findings suggest a genetic basis for disease development. One study found that the majority of patients with RA carry the epitope of the HLA-DRB1*04 cluster, and patients expressing 2 HLA-DRB1*04 alleles are at greater risk for nodular disease, major organ involvement, and surgery related to joint destruction.[1] Despite advances in our understanding of RA, there still remains a significant unmet medical need across key domains such as pain and physical function as well as increased morbidity and mortality among patients with RA compared with the general population.[3,11] A study from Widdifield and colleagues looked at trends in mortality rates over a 10-year period among patients with RA and the general population. The study showed 40% to 50% more deaths among the RA cohort.[12]

Comorbidities

As a progressive inflammatory disease with articular and systemic effects, RA is

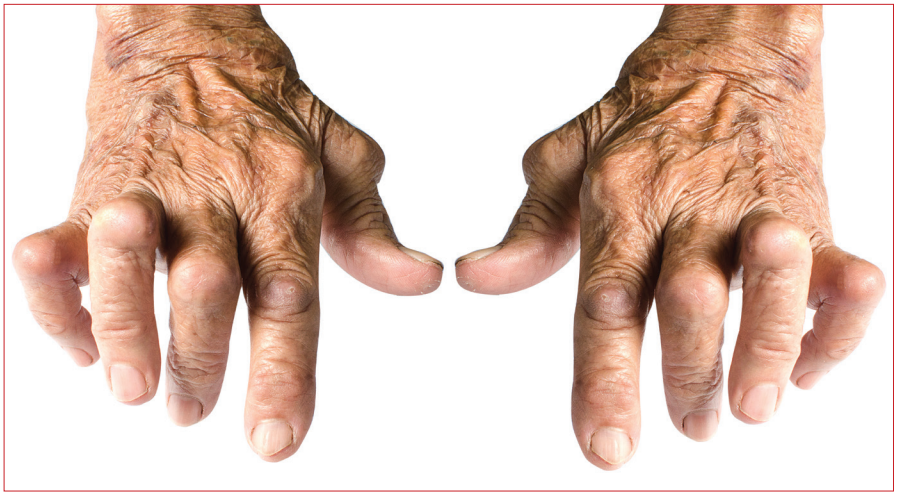
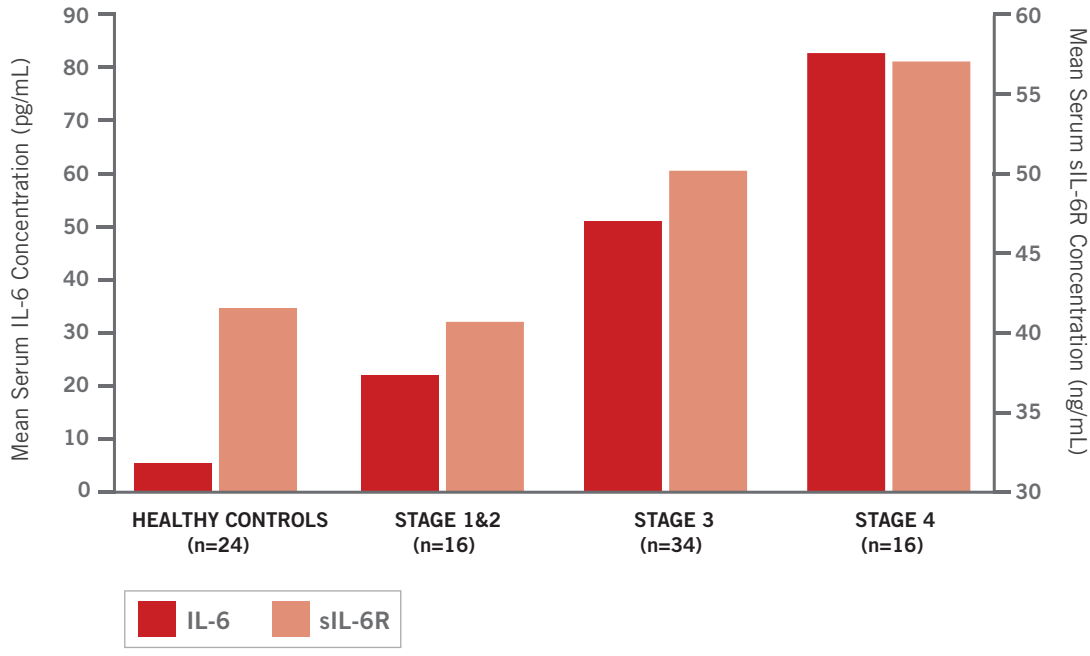


Image courtesy of Chaowalit Seeneha/shutterstock.com

Figure 1. Elevated levels of IL-6 and the soluble IL-6 receptor (sIL-6R) are associated with disease activity in RA



Source: Robak T, Gladalska A, Stepién H, Robak E. Serum levels of interleukin-6 type cytokines and soluble interleukin-6 receptor in patients with rheumatoid arthritis. *Mediators Inflamm*. 1998;7(5):347-353.

linked with several serious comorbidities that contribute to the disease burden (**Table 1**). The inflammatory processes in RA are associated with an increased risk of cardiovascular disease (CVD).[13] Hashizume and Mihara reported that life expectancy is reduced by up to 10 years due to CVD resulting from recurrent inflammation.[8] A separate study found that patients with RA have an approximately 2-fold greater CVD risk compared with the general population.[14] Data from the Consortium of Rheumatology Researchers of North America that followed patients with RA for a median of 2.7 years showed a reduced risk of CVD events with improved disease activity, underscoring the importance of inflammation control for CVD risk.[10]

Osteoporosis has been identified as a common systemic manifestation of RA, resulting in elevated risk of bone fracture.[1] Cutolo and colleagues assessed disease burden in RA and found that the risk of hip fracture was increased by 2-fold and vertebral fracture by 2.4-fold relative to patients without RA.[14]

RA is connected with a higher risk of infection, most commonly tuberculosis. This increased risk may be attributed to either impaired immune function related to the disease or the effects of drug therapies used in treatment.[4,14] In a population-based cohort of RA patients, infections requiring hospitalization were more common. Sites of infection with the highest risk for RA patients were bones, joints, soft tissues, and the respiratory tract.[14]

Individuals with RA also have an increased risk of certain cancers including lung and lymphoproliferative malignancies. A meta-analysis suggested that patients with RA have a 2-fold increase in the risk of lymphoma and a 63% increased risk of lung cancer compared with the general population.[4,14]

Furthermore, a higher prevalence of mental health conditions has been observed in RA populations, with reported estimates of 13% to 20% of individuals experiencing depression.[1,14]

Economic Toll

RA has significant economic implications for all stakeholders in terms of direct and indirect medical costs. Recent estimates calculate the annual health care expenditures for RA at $128 billion in the United States.[7,15] From a payer's perspective, Kawatkar and colleagues found that the total annual per-patient per-year cost of RA was $13,012 vs $4950 for patients without RA. The RA cohort also had a substantially higher pharmacy cost of $5825 that was on average $1380 higher than the control group.[16]

The cost of drug therapies for RA is also a key consideration for managed care payers. A recent retrospective analysis of claims data for approximately 25,000 patients in a large health benefit organization assessed the cost of biologics in the treatment of autoimmune disorders. The researchers found that the cost of biologics for RA ranged from $14,334 to $26,620 in the first year post index per treated patient.[17]

The high overall health care costs of RA are also attributed to increased hospitalizations, joint surgery, and other types of health care resource utilization.[15,18] According to the 2012 Nationwide Inpatient Survey, there were 9100 hospitalizations with an RA diagnosis, totaling $374 million in hospitalization costs (with an average cost of $41,000 per person).[4]

Stakeholders also need to consider the economic burden of comorbidities in patients with RA for their potential impact on patient care and outcomes. A study that assessed resource utilization and direct health care costs associated with RA and comorbid

conditions found that adjusted mean annual health care costs were highest for patients with RA and CVD ($14,145); followed by RA, CVD, and depression ($13,513); and RA and depression ($12,225).[7]

IL-6: A Cytokine Signaling Pathway in RA

Pro- and anti-inflammatory cytokines are involved in the pathology of RA. As a common chronic form of inflammatory arthritis, RA is driven by a complex network of cytokines that extends well beyond the joints.[1,2] The IL-6 protein is an important multifunctional cytokine that has been identified as a contributor of articular and systemic manifestations of RA, with high levels expressed in synovial fluids, synovial tissue, and blood.[1,2,19-21] While normal levels are important for the homeostasis in the inflammatory process, persistent, elevated IL-6 levels may play a role in disrupting homeostasis by impacting the function of a broad range of cells and physiologic processes.[1,22-29] IL-6 has also been shown to activate inflammatory pathways.[1]

IL-6 Is an Important Cytokine

Normal levels of cytokines and other signaling molecules are essential for homeostasis with regard to the inflammatory process.[27,30] Numerous pro-inflammatory cytokines, including TNF-α, IL-1, -4, -6, -13, -17, and -21, and interferons, play a key role in inflammatory diseases.[27,31] IL-6 also represents a critical node in the inflammatory cytokine network. Among conditions with autoimmunity and chronic inflammation, increased levels of IL-6 can interrupt homeostasis in many physiologic processes and contribute to chronic inflammation and disease progression.[1,27,29-37]

In response to infection or injury, IL-6 signaling helps promote and coordinate the pro-inflammatory activities of cells throughout the body.[27,30,32] IL-6 can also promote systemic inflammation through its actions in the liver, which increases hepatic production of acute phase reactants involved in the pro-inflammatory cascade.[27,38] Studies have shown that IL-6 can mediate fever by crossing the blood-brain barrier and initiating synthesis of prostaglandin E2 in the hypothalamus, thereby regulating body temperature.[39-41] Dayer and Choy offered a perspective on how IL-6 can induce articular and systemic symptoms of RA and concluded that IL-6 is found in abundance in the serum and synovial fluid of inflamed joints in patients with RA, and the elevated levels correlate with disease activity and joint destruction.[27]

Transient or persistent increases of IL-6 levels are seen in a variety of conditions ranging from infection/trauma (transient increase) to RA (persistent disease). Under normal conditions, circulating levels of IL-6 are maintained at low levels among healthy individuals, with serum IL-6 levels ranging from ~1 pg/mL to ~16 pg/mL.[42-46] In response to serious infection, serum IL-6 levels may reach 10,000 pg/mL, with significant, albeit less dramatic, increases reported in other inflammatory and infectious diseases.[45,47,48] Among patients with RA, studies reported variations in serum IL-6 levels ranging from 5 pg/mL to 200 pg/mL, with 100- to 10,000-fold higher concentrations observed in synovial fluid.[43-45,49-51]

Table 1. Comorbidities Associated With RA[1,4,8,10,13,14]

Cardiovascular disease
Osteoporosis
Anemia
Infection
Malignancies
Mental health conditions (eg, depression and anxiety)
Fatigue
Cognitive dysfunction

Table 2. Processes Potentially Impacted by IL-6

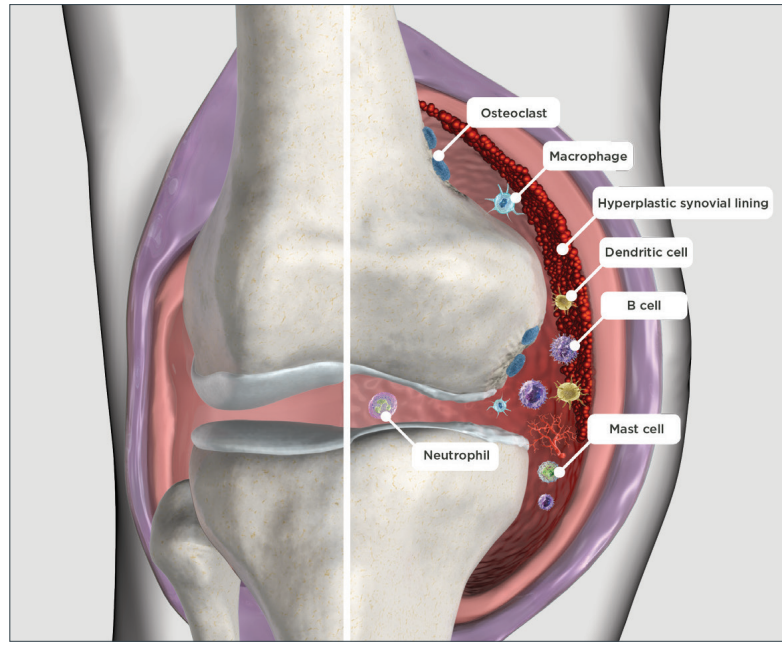
Adipocytes
• Lipid metabolism through interaction with adipose tissue[8,79]
• Low-density lipoprotein cholesterol metabolism[73]
Liver
• Systemic inflammation, via its actions on the liver, which increases C-reactive protein (CRP) and serum amyloid A levels[1]
Heart
• Inducer of CRP[27]
• Vascular endothelial dysfunction[13,27]
Red Blood Cells
• Hypoferremia through induction of hepcidin—a potential cause of anemia[1]
• Anemia of chronic disease[1]
• Fatigue[1]
Bone
• Osteoclast activation[1]
• Generalized bone mineral density loss[58]
Immune Cell
• Autoantibody production[27]
• Dysregulation of T cells and B cells[21,27,58]

Elevated IL-6 Levels and RA Progression

Persistent elevated IL-6 levels have been associated with RA progression, including disease activity, articular destruction, and systemic manifestations.[27] Additionally, increased IL-6 levels have been identified in chronic inflammation and disease progression in RA. It may also affect metabolism (ie, lipid, glucose), hematopoiesis, the central nervous system, and host defense.[27,32-34] For example, studies have demonstrated that IL-6 affects lipid metabolism by stimulating hepatic fatty acid synthesis and adipose tissue lipolysis. IL-6 also increases cholesterol synthesis while lowering cholesterol secretion.[27]

Robak and colleagues demonstrated that higher concentrations of IL-6 and the soluble IL-6 receptor in patients with RA are associated with disease activity compared with healthy individuals (**Figure 1**).[52]

Figure 2. IL-6–activated FLS cells play a key role in chronic inflammation and joint destruction in RA



There is an influx of immune cell mediators and increased cytokine signaling between the cells in the synovium that leads to inflammation and eventual structural joint damage through increased osteoclast activities.

Abbreviation: FLS, fibroblast-like synoviocyte.

Source: Choy EH, Kavanaugh AF, Jones SA. The problem of choice: current biologic agents and future prospects in RA. *Nat Rev Rheumatol*. 2013;9(3):154-163.

Articular and Systemic Manifestations of RA

Several studies have explored the central role elevated IL-6 plays in the articular manifestations of RA.[22,27,53,54] Elevated IL-6 perpetuates chronic synovitis (based on pre-clinical, *ex vivo*, and clinical data).[11,27,44] Chronic synovitis is the dominant feature of RA, often leading to irreversible destruction of cartilage and bone erosion.[11,55] It does this in 3 ways:

- Activates pro-inflammatory cells and mediators within the joints, including neutrophils, macrophages, fibroblast-like synoviocyte (FLS) cells, T cells, and B cells[21,54-60]
- Degrades cartilage by triggering FLS and chondrocytes to release cathepsins and matrix metalloproteinases (MMPs)[3,61-64]
- Stimulates osteoclastogenesis and osteoclast activity, leading to structural damage through bone resorption. Evidence also indicates that IL-6 and/or sIL-6R is implicated in the regulation of osteoclast precursors in the bone marrow prior to and during inflammatory arthritis[53,54,58,64-66]

Serum IL-6 levels peak in the early morning hours when patients with RA most often exhibit painful joint stiffness as well as functional disability.[19,67,68] In samples taken every hour over a 24-hour period, Crofford and colleagues found that early morning levels of IL-6 were nearly 4 times higher in 5 patients with RA compared with 5 patients without the disease (0.55 pmol/L vs 0.15 pmol/L, respectively).[19]

Researchers have also determined that IL-6–activated FLS cells play a crucial role in chronic inflammation and joint destruction[3,31,69] (**Figure 2**). IL-6 activates and increases proliferation of FLS cells of the synovial initial, or inner lining.[22,57,69,70] In one study, synovial tissue samples and radiographs from patients with RA and osteoarthritis showed that the invasive properties of FLS cells correlated with radiologic and histologic damage in patients with RA.[71]

Effects of Elevated IL-6 Levels

The effects of persistently elevated IL-6 levels may play a role in systemic manifestations of RA.[1,19,34] **Table 2** lists some of the organs and cells affected by IL-6. Researchers have examined this role and have studied IL-6 as a possible mediator of metabolic processes.[72] For example, the function of IL-6 in lipid metabolism in adipocytes (ie, cells found in connective tissue that are specialized for the storage of fat) has been shown to have lipolytic properties, which is the chemical breakdown of fat.[8] A separate study found that one mechanism by which IL-6 affects lipid metabolism is the upregulation of low-density lipoprotein (LDL)-receptor in hepatic cells, which may eventually lead to a lowering in LDL cholesterol plasma levels.[73]

IL-6 plays an important role in the defense of the liver from infection. It is also a potent liver cell transformer, inducing mitosis, and is implicated in the metabolic function of the liver.[74]

Like the liver, the heart also is affected by IL-6. As a pro-inflammatory mediator, IL-6 spurs inflammation. The presence of C-reactive protein (CRP) is augmented with inflammation. Studies have shown that an increase in IL-6 and CRP has been associated with an increased cardiovascular risk in healthy individuals.[27] The circulating

of IL-6 can also result in endothelial dysfunction, which can be manifested as an imbalance between vasodilating and vasoconstricting substances (ie, the widening and narrowing of blood vessels).[13] Even during a latent state of RA, systemic levels of cytokines, such as IL-6, can continue to support CVD.[13]

Hypoferremia, which is an iron deficiency in the circulating blood, is triggered by hepcidin, a protein secreted by the liver that in elevated levels can prevent iron from being taken up by red blood cells. IL-6 is required for the release of hepcidin. Hepcidin has also been identified as a significant mediator of anemia in patients with chronic disease.[1] Additionally, persistent fatigue is observed in individuals with RA, which is primarily mediated by upregulation of various cytokines such as IL-6.[1]

Osteoclast activation is yet another effect of IL-6. The primary function of osteoclasts is the repair, maintenance, and remodeling of bones. IL-6, however, can cause an imbalance between bone resorption and bone formation.[1] Studies have shown that IL-6 is negatively associated with bone mineral density.[58]

IL-6 has also been linked to immune cell disruption; it plays a role in B cell and T cell development.[21,27,58]

IL-6 Signaling Mechanisms

IL-6 signals through 2 distinct mechanisms: membrane-bound receptors (classical or cis-signaling) and soluble forms of its receptors (trans-signaling).[6,27,75-78] Together, these signaling mechanisms allow IL-6 to interact with cells that do or do not express the IL-6 membrane-bound receptor (mIL-6R).[75]

In classical or cis-signaling, IL-6 binds to mIL-6R, and then the mIL-6R complex binds to glycoprotein 130 (gp130) subunits.[27] In trans-signaling, IL-6 binds to its sIL-6R, which is present in serum and synovial fluid.[6] When bound to IL-6, sIL-6R can communicate and signal in any cell type that expresses gp130.[27,30,75] Then, the sIL-6R complex binds to gp130.[27,30]

It is important to understand how cis- and trans-signaling elicit their effects through the IL-6 and IL-6R. These complexes activate the Janus kinase-signal transducer and activator of transcription pathway and the mitogen-activated pathway-inducing the expression of pro-inflammatory genes such as MMP and receptor activator of NF-κB ligand.[27,31,61] IL-6 signaling is a major contributor to the induction of CRP and other acute-phase proteins. Finally, the acute-phase response changes the concentration of certain plasma proteins, such as CRP, hepcidin, and serum amyloid A, that are produced in the liver in response to infections, tissue injury, neoplastic growth, or immunological disorders.[23,24,27]

Conclusion

RA is a heterogeneous disease that presents significant clinical consequences and economic burden for stakeholders. As a better understanding of the signaling pathways involved in the pathogenesis of RA has been elucidated in the literature, it has shown that IL-6 is one of the cytokines that plays an important role in RA.

References

1. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology (Oxford).* 2012;51(suppl 5):v3-v11.
2. Schmitz ML, Weber A, Roxlau T, Gaestel M, Kracht M. Signal integration, crosstalk mechanisms and networks in the function of inflammatory cytokines. *Biochem Biophys Acta*. 2011;1813(12):2165-2175.
3. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. *Immunol Rev*. 2010;233(1):233-255.
4. Centers for Disease Control and Prevention. *Rheumatoid Arthtritis (RA)*. http://www.cdc.gov/arthritis/basics/rheumatoid.htm. Accessed December 3, 2016.
5. Roberts CA, Dickinson AK, Taams LS. The interplay between monocytes/macrophages and CD4(+) T cell subsets in rheumatoid arthritis. *Front Immunol*. 2015;6:571.
6. Mihara M, Hashizume M, Yoshida H, Suzuki M, Shiina M. IL-6/IL-6 receptor system and its role in physiological and pathological conditions. *Clin Sci (Lond)*. 2012;122(4):143-159.
7. Owens GM. Managed care implications in managing rheumatoid arthritis. *Am J Manag Care*. 2014;20(7 suppl):S145-S152.
8. Hashizume M, Mihara M. The roles of interleukin-6 in the pathogenesis of rheumatoid arthritis. *Arthritis*. 2011;2011:765624.
9. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023-2038.
10. Solomon DH, Reed GW, Kremer JM, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheumatol*. 2015;67(6):1449-1455.
11. Choy E. Inhibiting interleukin-6 in rheumatoid arthritis. *Curr Rheumatol Rep*. 2008;10(5):413-417.
12. Widdifield J, Bermatsky S, Paterson JM, et al. Trends in excess mortality among patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2015;67(8):1047-1053.
13. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation*. 2003;108(24):2957-2963.
14. Cutolo M, Kitas GD, van Riel PL. Burden of disease in treated rheumatoid arthritis patients: going beyond the joint. *Semin Arthritis Rheum*. 2014;43(4):479-488.
15. Alemao E, Joo S, Kawabata H, et al. Effects of achieving target measures in rheumatoid arthritis on functional status, quality of life, and resource utilization: analysis of clinical practice data. *Arthritis Care Res (Hoboken)*. 2016;68(3):308-317.
16. Kawatkar AA, Jacobsen SJ, Levy GD, Medhekar SS, Venkatasubramaniam KV, Herrinton LJ. Direct medical expenditure associated with rheumatoid arthritis in a nationally representative sample from the medical expenditure panel survey. *Arthritis Care Res (Hoboken)*. 2012;64(11):1649-1656.
17. Gu T, Shah N, Deshpande G, Tang DH, Eisenberg DF. Comparing biologic cost per treated patient across indications among adult US managed care patients: a retrospective cohort study. *Drug Real World Outcomes*. 2016;3(4):369-381.
18. Metsios GS, Stavropoulos-Kalinoglou A, Treharne GJ, et al. Disease activity and low physical activity associated with number of hospital admissions and length of hospitalisation in patients with rheumatoid arthritis. *Arthritis Res Ther*. 2011;13(3):R108.
19. Crofford LJ, Kalogeras KT, Mastorakos G, et al. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J Clin Endocrinol Metab*. 1997;82(4):1279-1283.
20. Madhok R, Crilly A, Watson J, Capell HA. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. *Ann Rheum Dis*. 1993;52(3):232-234.
21. de Hooge AS, van De Loo FA, Arntz OJ, van Den Berg WB. Involvement of IL-6, apart from its role in immunity, in mediating a chronic response during experimental arthritis. *Am J Pathol*. 2000;157(6):2081-2091.
22. Ito A, Itoh Y, Sasaguri Y, Morimatsu M, Mori Y. Effects of interleukin-6 on the metabolism of connective tissue components in rheumatoid

synovial fibroblasts. *Arthritis Rheumatol*. 1992;35(10):1197-1201.
23. Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds. *Rheumatology*. 5th ed. Philadelphia, PA: MOSBY Elsevier Ltd; 2011.
24. Janeway CJ, Travers P, Walport M, Shlomchik M. Immunobiology: *The Immune System in Health and Disease*. 5th ed. New York, NY: Garland Science; 2001.
25. Jansen JH, Kluin-Nelemans JC, Van Damme J, Wientjens GJ, Willemze R, Fibbe WE. Interleukin 6 is a permissive factor for monocytic colony formation by human hematopoietic progenitor cells. *J Exp Med*. 1992;175(4):1151-1154.
26. Okada A, Yamasaki S, Koga T, et al. Adipogenesis of the mesenchymal stromal cells and bone oedema in rheumatoid arthritis. *Clin Exp Rheumatol*. 2012;30(3):332-337.
27. Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. *Rheumatology (Oxford)*. 2010;49(1):15-24.
28. Liang KP, Myasoedova E, Crowson CS, et al. Increased prevalence of diastolic dysfunction in rheumatoid arthritis. *Ann Rheum Dis*. 2010;69(9):1665-1670.
29. Rho YH, Chung CP, Oeser A, et al. Inflammatory mediators and premature coronary atherosclerosis in rheumatoid arthritis. *Arthritis Rheumatol*. 2009;61(11):1580-1585.
30. McInnes IB. Cytokines. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, eds. *Kelley's Textbook of Rheumatology*. Vol 1. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013:369-381.
31. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol*. 2007;7(6):429-442.
32. Saxena A, Cronstein BN. Acute phase reactants and the concept of inflammation. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, eds. *Kelley's Textbook of Rheumatology*. Vol 1. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013:818-829.
33. Tutuncu Z, Kavanaugh A. Anticytokine therapies. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, eds. *Kelley's Textbook of Rheumatology*. Vol 1. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013:957-977.
34. Tanaka T, Kishimoto T. Targeting interleukin-6: all the way to treat autoimmune and inflammatory diseases. *Int J Biol Sci*. 2012;8(9):1227-1236.
35. Bode JG, Albrecht U, Häussinger D, Heinrich PC, Schaper F. Hepatic acute phase proteins–regulation by IL-6- and IL-1-type cytokines involving STAT3 and its crosstalk with NF-kB-dependent signaling. *Eur J Cell Biol*. 2012;91(6-7):496-505.
36. Alesci S, Martinez PE, Kelkar S, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *J Clin Endocrinol Metab*. 2005;90(5):2522-2530.
37. Raison CL, Borisov AS, Majer M, et al. Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression. *Biol Psychiatry*. 2009;65(4):296-303.
38. Castell JV, Gómez-Lechón MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. *Hepatology*. 1990;12(5):1179-1186.
39. Sundgren-Andersson AK, Ostlund P, Bartfai T. IL-6 is essential in TNF-alpha-induced fever. *Am J Physiol*. 1998;275(6 pt 2):R2028-R2034.
40. Dinarello CA, Cannon JG, Mancilla J, Bishai I, Lees J, Coceani F. Interleukin-6 as an endogenous pyrogen: induction of prostaglandin E2 in brain but not in peripheral blood mononuclear cells. *Brain Res*. 1991;562(2):199-206.
41. Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J Clin Endocrinol Metab*. 1993;77(6):1690-1694.
42. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? *Exerc Immunol Rev*. 2006;12:6-33.
43. Desgeorges A, Gabay C, Silacci P, et al. Concentrations and origins of soluble interleukin 6 receptor-alpha in serum and synovial fluid. *J Rheumatol*. 1997;24(8):1510-1516.
44. Sack U, Kinne RW, Marx T, Heppt P, Bender S, Emmrich F. Interleukin-6 in synovial fluid is closely associated with chronic synovitis in rheumatoid arthritis. *Rheumatol Int*. 1993;13(2):45-51.
45. Pujhari SK, Prabhakar S, Ratho R, et al. Th1 immune response takeover among patients with severe Japanese encephalitis infection. *J Neuroimmunol*. 2013;263(1-2):133-138.
46. Motivala SJ, Sarfatti A, Olmos L, Irwin MR. Inflammatory markers and sleep disturbance in major depression. *Psychosom Med*. 2005;67(2):187-194.
47. Friedland JS, Suputtamongkol Y, Remick DG, et al. Prolonged elevation of interleukin-8 and interleukin-6 concentrations in plasma and of leukocyte interleukin-8 mRNA levels during septicemic and localized *Pseudomonas pseudomallei* infection. *Infect Immun*. 1992;60(6):2402-2408.
48. Wang SM, Liao YT, Hu YS, et al. Immunophenotype expressions and cytokine profiles of influenza A H1N1 virus infection in pediatric patients in 2009. *Dis Markers*. 2014;2014:195453.
49. Usón J, Balsa A, Pascual-Salcedo D, et al. Soluble interleukin 6 (IL-6) receptor and IL-6 levels in serum and synovial fluid of patients with different arthropathies. *J Rheumatol*. 1997;24(11):2069-2075.
50. Hein GE, Köhler M, Oelzner P, Stein G, Franke S. The advanced glycation end product pentosidine correlates to IL-6 and other relevant inflammatory markers in rheumatoid arthritis. *Rheumatol Int*. 2005;26(2):137-141.
51. Sacerdote P, Carrabba M, Galante A, Pisati R, Manfredi B, Panerai AE. Plasma and synovial fluid interleukin-1, interleukin-6 and substance P concentrations in rheumatoid arthritis patients: effect of the nonsteroidal anti inflammatory drugs indomethacin, diclofenac and naproxen. *Inflamm Res*. 1995;44(11):486-490.
52. Robak T, Gladalska A, Stepién H, Robak E. Serum levels of interleukin-6 type cytokines and soluble interleukin-6 receptor in patients with rheumatoid arthritis. *Mediators Inflamm*. 1998;7(5):347-353.
53. Kotake S, Sato K, Kim KJ, et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. *J Bone Miner Res*. 1996;11(1):88-95.
54. Wong PK, Quinn JM, Sims NA, van Nieuwenhuijze A, Campbell IK, Wicks IP. Interleukin-6 modulates production of T lymphocyte-derived cytokines in antigen-induced arthritis and drives inflammation-induced osteoclastogenesis. *Arthritis Rheumatol*. 2006;54(1):158-168.
55. van Leeuwen MA, Westra J, Limburg PC, van Riel PL, van Rijswijk MH. Interleukin-6 in relation to other proinflammatory cytokines, chemotactic activity and neutrophil activation in rheumatoid synovial fluid. *Ann Rheum Dis*. 1995;54(1):33-38.
56. Nakamura I, Omata Y, Naito M, Ito K. Blockade of interleukin 6 signaling induces marked neutropenia in patients with rheumatoid arthritis. *J Rheumatol*. 2009;36(2):459-460.
57. Hashizume M, Hayakawa N, Mihara M. IL-6 trans-signaling directly induces RANKL on fibroblast-like synovial cells and is involved in RANKL induction by TNF-alpha and IL-17. *Rheumatology (Oxford)*. 2008;47(11):1635-1640.
58. Maggio M, Guralnik J, Longo DL, Ferrucci L. Interleukin-6 in aging and chronic disease: a magnificent pathway. *J Gerontol A Biol Sci Med Sci*. 2006;61(6):575-584.
59. Chomarat P, Banchereau J, Davoust J, Palucka AK. IL-6 switches the differentiation of monocytes from dendritic cells to macrophages. *Nat Immunol*. 2000;1(6):510-514.

60. Ducreux J, Durez P, Galant C, et al. Global molecular effects of tocilizumab therapy in rheumatoid arthritis synovium. *Arthritis Rheumatol*. 2014;66(1):15-23.
61. Choy EH, Kavanaugh AF, Jones SA. The problem of choice: current biologic agents and future prospects in RA. *Nat Rev Rheumatol*. 2013;9(3):154-163.
62. Firestein GS. Invasive fibroblast-like synoviocytes in rheumatoid arthritis. Passive responders or transformed aggressors? *Arthritis Rheumatol*. 1996;39(11):1781-1790.
63. Rowan AD, Koshy PJ, Shingleton WD, et al. Synergistic effects of glycoprotein 130 binding cytokines in combination with interleukin-1 on cartilage collagen breakdown. *Arthritis Rheumatol*. 2001;44(7):1620-1632.
64. Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. *Arthritis Rheumatol*. 2010;62(1):33-43.
65. Ishimi Y, Miyaura C, Jin CH, et al. IL-6 is produced by osteoblasts and induces bone resorption. *J Immunol*. 1990;145(10):3297-3303.
66. Palmqvist P, Persson E, Conaway HH, Lerner UH. IL-6, leukemia inhibitory factor, and oncostatin M stimulate bone resorption and regulate the expression of receptor activator of NF-kappa B ligand, osteoprotegerin, and receptor activator of NF-kappa B in mouse calvariae. *J Immunol*. 2002;169(6):3353-3362.
67. Arvidson NG, Gudbjörnsson B, Elfman L, Rydén AC, Tötterman TH, Hällgren R. Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. *Ann Rheum Dis*. 1994;53(8):521-524.
68. Gibbs JE, Ray DW. The role of the circadian clock in rheumatoid arthritis. *Arthritis Res Ther*. 2013;15(1):205.
69. Bottini N, Firestein GS. Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors. *Nat Rev Rheumatol*. 2013;9(1):24-33.
70. Choe JY, Park KY, Park SH, Lee SI, Kim SK. Regulatory effect of calcineurin inhibitor, tacrolimus, on IL-6/sIL-6R-mediated RANKL expression through JAK2-STAT3-SOCS3 signaling pathway in fibroblast-like synoviocytes. *Arthritis Res Ther*. 2013;15(1):R26.
71. Tolboom TC, van der Helm-van Mil AH, Nelissen RG, Breedveld FC, Toes RE, Huizinga TW. Invasiveness of fibroblast-like synoviocytes is an individual patient characteristic associated with the rate of joint destruction in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2005;52(7):1999-2002.
72. Hashizume M, Mihara M. IL-6 and lipid metabolism. *Inflammation and Regeneration*. 2011;31(3):325-333.
73. Gierens H, Nauck M, Roth M, et al. Interleukin-6 stimulates LDL receptor gene expression via activation of sterol-responsive and Sp1 binding elements. *Arterioscler Thromb Vasc Biol*. 2000;20(7):1777-1783.
74. Schmidt-Arras D, Rose-John S. IL-6 pathway in the liver: from physiopathology to therapy. *J Hepatol*. 2016;64(6):1403-1415.
75. Rose-John S, Scheller J, Elson G, Jones SA. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. *J Leukoc Biol*. 2006;80(2):227-236.
76. Hermanns HM, Müller-Newen G, Heinrich PC, Haan S. Bow to your partner for signaling. *Nat Struct Mol Biol*. 2005;12(6):476-478.
77. Boulanger MJ, Chow DC, Brevnova EE, Garcia KC. Hexameric structure and assembly of interleukin-6/IL-6 alpha-receptor/gp130 complex. *Science*. 2003;300(5628):2101-2104.
78. Skiniotis G, Boulanger MJ, Garcia KC, Walz T. Signaling conformations of the tall cytokine receptor gp130 when in complex with IL-6 and IL-6 receptor. *Nat Struct Mol Biol*. 2005;12(6):545-551.
79. Trujillo ME, Sullivan S, Harten I, Schneider SH, Greenberg AS, Fried SK. Interleukin-6 regulates human adipose tissue lipid metabolism and leptin production *in vitro*. *J Clin Endocrinol Metab*. 2004;89(11):5577-5582.