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Review Article

Targeting IL-6 Signaling Pathways for Musculoskeletal Disorders Treatment: Risks and Benefits

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Abstract

Pro-inflammatory mediators like IL-6 effectively mediated the majority of musculoskeletal disorders such rheumatoid arthritis (RA), osteoarthritis (OA), and tendinitis. Increased levels of IL-6 are found in the serum or synovial fluid of patients with these disorders, and these levels are correlated with the incidence and severity of the disease. IL-6 is crucial for the development of cartilage pathology, for example, by inducing a variety of pathways that are involved in the induction and spread of inflammation. The expression of anti-catabolic factors is similarly increased by IL-6, indicating a protective function. The differential impacts of IL-6 classic and trans-signaling may be the reason for this dual role of IL-6, which has so far remained poorly understood. In this article, the experimental and clinical data on the function of inhibiting IL-6 signaling in the development and progression of pathologies of the synovium, cartilage, and bones were thoroughly reviewed. By evaluating the IL-6 targeting approaches that are currently being considered in research and clinical practice, it may provide a glimpse into the future of these illnesses' treatment.

Keywords: Interleukin-6, IL-6 receptors, Musculoskeletal disorders, IL-6 antagonists

استهداف مسارات إشارات IL-6 لعلاج الاضطرابات العضلية الهيكلية: المخاطر والفوائد

الخلاصة

تساهم محفزات الالتهابات مثل IL-6 بشكل فعال في غالبية الاضطرابات العضلية الهيكلية مثل التهاب المفاصل الرثوي (RA) والتهاب العظام (OA) والأوتار. تم العثور على مستويات متزايدة من IL-6 في المصل أو السائل الزليلي للمرضى الذين يعانون من هذه الاضطرابات، وترتبط هذه المستويات مع حدوث وشدة المرض. IL-6 مهم لتطور أمراض الغضروف عن طريق إحداث مجموعة متنوعة من المسارات التي تشارك في تحريض وانتشار الالتهاب. ويتم زيادة تكوين العوامل المضادة للهدم الأيضي بواسطة IL-6 كوظيفة وقائية. قد تكون التأثيرات التفاضلية لـ IL-6 الكلاسيكية والإشارات العابرة هي السبب في هذا الدور المزدوج ، والذي ظل حتى الآن غير مفهوم بشكل جيد. في هذه المقالة تمت مراجعة البيانات التجريبية والسريرية حول تأثير تثبيط إشارات IL-6 في تطور أمراض الغشاء الزليلي والغضاريف والعظام. من خلال تقييم طرق استهداف IL-6 التي يتم النظر فيها حاليا في البحث والممارسة السريرية يمكن التوصل الى تفاصيل أكثر عن مستقبل علاج هذه الأمراض.

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INTRODUCTION

Interleukin (IL)-6 is a cytokine that was found to have pleiotropic effects [1]. It contributes to inflammation while also reducing inflammation [2]. Interleukin-6 (IL-6) has the capacity to activate B cells in the body. In addition to inducing the expression of a wide variety of proteins that are directly responsible for acute inflammation, it also plays an important part in the proliferation and differentiation of cells within the human body [3]. IL-6 is a soluble mediator with a pleiotropic effect, which means it affects hematopoiesis, inflammation, and the immune system [4], and specifically, it has an effect on these three processes. In terms of its chemical composition, it can be described as a glycopeptide that is produced in the secretion process and has a molar mass of 25 KD and a chain length of 184 amino acids [5]. Interferon (IFN-2), hepatocyte-stimulating factor, hybridoma and plasmacytoma growth factor, and interleukin-6 are all names for this substance [6]. This cytokine's anti-inflammatory and metabolic activity is responsible for the adaptation that occurs in response to the intense training that occurs during exercise [7]. A surge in the release of this cytokine can be a foundation for the pathogenesis of musculoskeletal diseases and other conditions such as cytokine release syndrome (CRS) [8]. In contrast, IL-6 takes on pro-inflammatory activity when there is no control over its production. When IL-6 is present at homeostatic levels, it is responsible for the resolution of tissue lesions [9], but when its levels are amplified, it causes a cytokine storm [10]. IL-6 is a pro-inflammatory cytokine with a pleiotropic molecular weight of 25 kD and 184 amino acids [11]. It is characterized by the presence of four helices [12]. Both the IL-6 receptors (IL-6Rs) and the IL-6-mediated signaling can be broken down into two distinct categories. Both soluble (sIL-6R) and membrane-bound (mIL-6R) IL-6 receptors have been identified [13], and IL-6-related signaling can take the form of either trans- or traditional cis-signaling. On the surface of immune cells, mIL-6R is found to be selectively expressed [14]. Classical signaling occurs when IL-6 binds with mIL-6R to form a complex. This complex then binds to the transmembrane protein glycoprotein 130 (gp-130), thereby completing the signal transduction and taking on a role that is pro-inflammatory [15]. During the trans-signaling process, IL-6 is shown to interact with sIL-6R, and forms a complex that then binds to gp-130. Janus kinase (JAK) and signal transducer and activator of transcription 3 (STAT3) are the proteins responsible for the final complex interactions, which transduce signaling within the cytosol [16]. gp-130-bounded JAK is responsible for the phosphorylation of STAT3 in the cytosol, and the phosphorylated STAT3 then moves into the nucleus to perform its role as a transcription activator [17] (Figure 1).

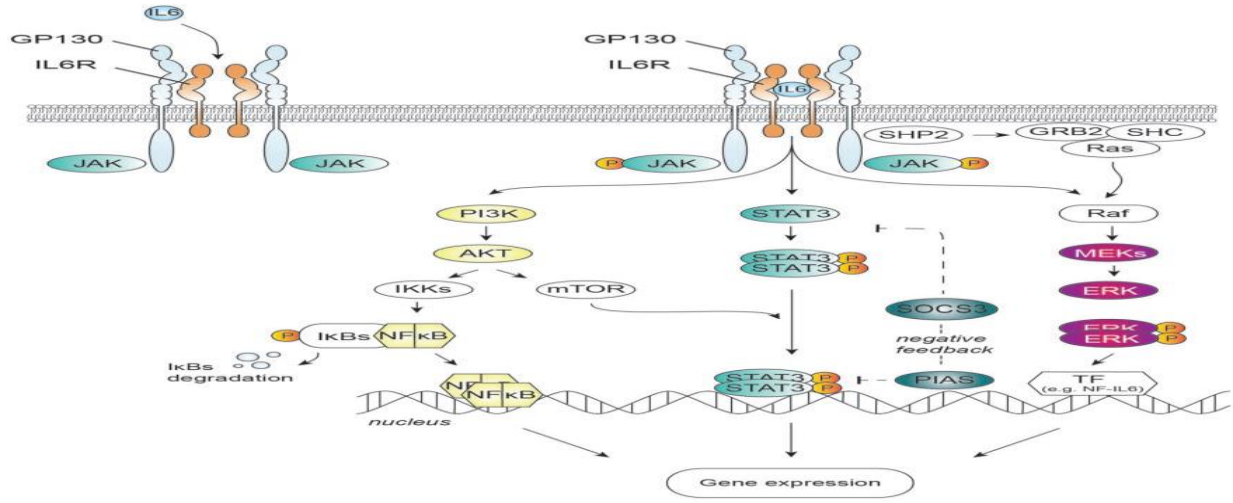

Figure 1: Molecular view describing the IL-6 signaling pathways. Following IL-6's binding to the IL-6R, the creation of a complex with gp130 starts the phosphorylation of JAKs, which activates STAT3-, PI3K-, Ras-Raf-MEK-ERK signaling. In order to control the expression of the target gene, activated transcription factors, such as STAT3, NFκB, and NF-IL-6, translocate to the nucleus. By preventing JAK-mediated activation of STAT3 (SOCS3) or STAT3's DNA-binding ability, SOCS and PIAS proteins inhibit the JAK-STAT signal that is brought on by IL-6 (PIAS). gp130: glycoprotein 130; IL-6: interleukin-6; JAK: janus kinase; MAPK: mitogen-activated protein kinase; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; NF-IL6: a nuclear factor for IL-6 expression; PIAS: protein inhibitors of activated STATs; PI3K: phosphoinositide 3-kinase; SOCS3: suppressor of cytokine signaling 3; STAT3: signal transducer and activator of transcription 3 [17].

Endothelial cells have been shown to express sIL-6R; such cells do not express mIL-6R [18]. The majority of cells that express mIL-6R are found in the immune system [2]. These immune cells include monocytes, macrophages, T cells, and neutrophils. When the STAT3 protein is activated, transcription of target genes such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF)-1α increases [19]. VEGF is a cytokine that has pro-angiogenic activities along with inflammatory and regulatory functions [20,21]. During the severe or acute phase of hypoxia, HIF-1alpha serves as an important mediator [22]. There are four potential extracellular targets to antagonize IL-6 signaling: IL-6 itself, IL-6R, gp130, and/or the IL-6/sIL-6R complex. Each of these targets can be antagonized individually or in combination [23]. Avimers, small molecules, and chimeric, humanized, or human monoclonal antibodies (mAbs) are some of the IL-6 targeting agents that have been developed in recent years [24]. At the moment, there are a variety of therapeutic approaches that can successfully target the IL-6 signaling pathway and are used in a secure manner for the treatment of a number of inflammatory diseases [25]. To cite just one example, the IL-6R targeting antibody tocilizumab has been shown to be effective in the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), Castleman's disease, and most recently, giant cell arteritis [3,26].

METHODS

Research articles that include experimental animal studies and clinical trials, and reviews published between January 2010 and September 2022 that were peer-reviewed were evaluated in three major search tools: PubMed, Google Scholar, and ResearchGate. Publications before January 2010 were also included if the initial reading of the literature suggested that these articles represented significant discoveries and/or had historical value. The keywords and key phrases employed were: IL-6 receptor, IL-6R antagonists, musculoskeletal disorder, risks and benefits, and chronic joints disorders. From the large number of publications collected, only those relevant to the content of this review were included in this review article.

RESULTS

Potential Role in Rheumatoid Arthritis

An abnormally high level of IL-6 production in the synovium leads to the development of chronic synovitis and the proliferation of fibroblast-like synoviocytes, which in turn promotes angiogenesis and cartilage degradation in the synovium [27]. This occurs during the pathogenesis of rheumatoid arthritis. The overproduction of IL-6 is another factor that contributes to these extra-articular manifestations as well as the comorbidities. Rheumatoid arthritis (RA) patients frequently experience extra-articular manifestations and comorbidities such as cardiovascular diseases, osteoporosis, and depression [28,29]. Inhibition of IL-6 by targeting IL-6R has not only been shown to be beneficial within the joint, but it has also been shown to be beneficial in extra-articular manifestations of synovium cartilage degradation [27]. This is due to the fact that IL-6 inhibition has been shown to be beneficial in both settings. Several clinical studies [30,31] have provided evidence to support this claim. Accordingly, experience of extra-articular manifestations can be regarded as common comorbidities in the vast majorities of patients, which include cardiovascular diseases, osteoporosis, depression, and many others [32,33]. In a number of clinical studies [28,34], IL-6 inhibition that targeted IL-6R demonstrated beneficial effects not only within the joint but also in the extra-articular manifestations of rheumatoid arthritis (RA). Tocilizumab and sarilumab are the two drugs that target IL-6R that are currently used in clinical practice for the treatment of musculoskeletal disorders with an autoimmune cause, such as RA [35]. Both of these drugs have been shown to be effective in reducing symptoms associated with these conditions. For instance, the humanized monoclonal antibody (mAb) tocilizumab received its initial approval for the treatment of Castleman's disease in the year 2005 in Japan [36]. Tocilizumab was subsequently granted approval by the FDA in 2010 for a variety of indications, including moderately to severely active RA in adults who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs) [37]. Among the other indications for which tocilizumab was granted approval by the FDA in 2010, moderately to severely active RA in adults was one of the indications. In stark contrast to the impressive results seen with IL-6R inhibitors, the development of RA treatments that target IL-6 has ground to a halt. IL-6R inhibitors are drugs that inhibit the activity of the IL-6 receptor. For instance, the most advanced anti-IL-6 ligand monoclonal antibody, known as Sirukumab, finished phase III trials but was not approved for use in the treatment of active RA by the United States Food and Drug Administration (FDA) in August 2017 due to safety concerns [38]. Olokizumab, which is another mAb against IL-6 for the treatment of RA, has shown promising results in phase II trials and is currently being tested in phase III trials [39]. These results are due to the fact that olokizumab has been shown to be effective in treating RA. HZ0408b is the name given to a novel humanized anti-IL-6 mAb that was developed not too long ago. With a high degree of specificity and relatively low

levels of cross-reactivity with other molecules, this monoclonal antibody binds to human IL-6 and renders it inactive [40]. It is well tolerated even at doses that can achieve therapeutic serum levels in the cynomolgus monkey [40], which means that it has excellent safety and efficacy profiles for the treatment of RA. In a patient with psoriatic arthritis who did not respond to treatment with the TNF inhibitor adalimumab, Kutsuna *et al*. (2022) discovered that administering the IL-6R antagonist tocilizumab as a second-line treatment helped keep the right elbow joint working. This was accomplished without the patient experiencing any adverse side effects. The patient has experienced complete clinical remission for the past 5 years and does not experience any limitations in their day-to-day life [41]. Additional evidence suggests that STAT3 signaling in keratinocytes, rather than in T cells, is a more significant determinant for psoriasis-like dermatitis. This psoriasis-like dermatitis is caused by a mechanism that involves upstream KC IL-6R signaling and downstream inhibition of type 1 immunity-associated C-X-C motif chemokine ligand 10 (CXCL10) responses. This was demonstrated by Ravipati *et al*. (2022) in an experimental study on animals, which showed that treatment of mice with the pan-Jak inhibitor, tofacitinib [42], led to the desired results. In addition, tofacitinib was used in a clinical study that was conducted by Valli *et al*. (2022) for a total of 16 patients who were suffering from active RA at the time that they were recruited. They discovered that there was a significant decrease in IL-6 levels, which they discovered to be linked to an improvement in the Disease Activity Score (DAS28) [43]. In this regard, the data of 2772 RA patients with abnormally elevated c-reactive protein (CRP) levels and low hemoglobin (Hb) values were analyzed. When compared with treatment with TNF inhibitors, the results showed that treatment with IL-6R inhibitors resulted in greater improvements in Hb levels and decreased CRP levels [44]. Anti-IL-6R medication is currently the most common treatment option for cancer patients who have immune checkpoint inhibitor-induced inflammatory arthritis and an inadequate response to glucocorticoids and methotrexate [45]. This treatment leads to an improvement in the condition of more than eighty percent of those patients. On the other hand, approximately half of them showed signs of the cancer spreading, and it is not yet known whether the biological DMARDs or the Janus kinase (JAK) pathway inhibitors had an effect on the way the tumor responded [45]. Despite the fact that many of the instances in which IL-6-targeting therapy was beneficial or partially effective still need to be confirmed through clinical studies, the therapy is recommended as a potential treatment option for a number of immunological disorders that are resistant to other forms of therapy.

Potential Role in Osteoarthritis and Tendonitis

It is becoming more widely accepted that inflammation is a factor in the development of osteoarthritis (OA), and this finding lends credence to the theory that synovium and inflammatory cytokines are to blame for the breakdown of cartilage [46,47]. Because of this, therapeutic efforts for osteoarthritis of the hand and knee have focused on inhibiting the pro-inflammatory cytokines TNF-α and IL-1β [48,49]. However, these efforts have not yet resulted in any practical applications. Additionally, IL-6 plays a significant role in the pathology of the joints in OA; however, IL-6 has not been the primary focus of research because IL-1β and TNF-α have garnered the most attention. Latourte *et al*. (2017) used an experimental model of osteoarthritis (OA) to investigate the effects of a systemic inhibition of interleukin 6 (IL-6), as well as signal transducer and activator of transcription (STAT3). A systemic blockade of IL-6 or STAT-3 was shown to be able to reduce the destabilization of the medial meniscus in mice with osteoarthritis (OA), according to the findings of the study [50]. Osteoarthritis synovial fluid (SF) contains both soluble IL-6R (sIL-6R) and signal transducing receptor gp130 (sgp130), but there has been no research done to compare these levels to those of healthy individuals [51]. Although significant levels of IL-6 are produced, it is still unknown whether the synovium is a source of soluble IL-6R in OA. This is despite the fact that IL-6 is produced. At this time, treatments for OA that target IL-6 signaling have not been approved for use. It is possible that this will soon change given that tocilizumab is currently being investigated in a phase 3 randomized controlled study in individuals with refractory hand OA (ClinicalTrials.gov NCT02477059). When a joint is injured, such as when the anterior cruciate ligament ruptures, the levels of IL-6 that are found in the synovial fluid (SF) skyrocket, sometimes by as much as a thousand times [52,53]. A similar increase in IL-6 levels has been observed following the destruction of localized cartilage [53]. This suggests that inhibiting IL-6 shortly after joint damage may be a promising therapeutic approach to stop the onset of posttraumatic OA; however, the ideal therapeutic window to stop more damage is still unknown at this time. In this regard, Wiegertjes *et al*. (2020) suggested that targeted reduction of IL-6 trans-signaling would be a better therapeutic approach, possibly preventing the detrimental effects of IL-6 on OA while maintaining protective IL-6 signaling via the classical pathway [54]. This was suggested in light of the fact that targeted reduction of IL-6 trans-signaling would be a more effective therapeutic approach. In a

collagenase-induced rat model of tendinopathy, Ko *et al*. (2022) investigate the therapeutic benefits of substance P inhibitor (SPI) on inflamed tenocytes. This model is used to study tendinopathy. The findings of this study showed that there was a significant difference in the mRNA levels of IL-6 between inflamed tenocytes and those that had been treated with SPI in a rat model of tendinopathy that was induced by collagenase. This provides evidence that a method such as this may have therapeutic effects on the process of tendon healing and restoration [55]. The most significant findings in this field are outlined in Table 1, which presents experimental and clinical evidence on the role of interference with IL-6 signaling as a potential preventive or therapeutic option for musculoskeletal disorders.

DISCUSSION

With the help of this literature review, the reader can obtain an update on the emerging evidence on agents that selectively target the IL-6 signaling pathway, including new data from 2010 onwards. This new information was included [56,57]. In hindsight, the range of possible indications has grown significantly over the past few years, and the availability of large-scale observational studies has provided researchers with the opportunity to acquire a comprehensive understanding of the effectiveness and long-term safety of these agents. It has been demonstrated to be effective in treating a wide range of inflammatory diseases, particularly musculoskeletal conditions such as rheumatoid arthritis (RA), osteoarthritis (OA), and tendinitis [58,59]. New information, particularly regarding RA, enabled us to improve treatment strategies involving tocilizumab and other agents [60]. A number of new compounds, including olokizumab and sirukumab, that target both the IL-6R and the IL-6 ligands have been shown to be clinically effective in treating rheumatoid arthritis (RA), according to a number of very significant new findings [32]. Sarilumab, the second IL-6R blocker for RA, was approved in 2017 due to consistent efficacy data [61]. Currently, only Russia has approved the humanized IL-6 ligand blocker olokizumab for the treatment of rheumatoid arthritis [62]. In 2017, the FDA eventually denied Sirukumab approval due to safety concerns [63]. In addition, strategic study results suggest that IL-6 pathway inhibitors may have some advantages over TNF-inhibitors for patients who do not qualify for conventional synthetic DMARD combination therapy. Tocilizumab monotherapy may be an effective option for RA patients. In contrast to the group that received both methotrexate and tocilizumab, the monotherapy group had a poorer clinical outcome and a more pronounced radiographic progression [64]. It is possible to taper concomitant methotrexate or steroids in patients with sustained low disease activity or remission, but there is a risk of a flare. It has been discovered that IL-6 is a critical indicator of cytokine storms and governs a number of elements of cellular inflammation and vascular homeostasis. Furthermore, the progression of serious illnesses like aging, cancer, and severe viral infections is linked to dysregulation or high levels of IL-6 in a patient's body [65]. They might be at fault if therapy doesn't work, which would have serious repercussions. Giving a patient an anti-IL-6 or anti-IL-6R antibody can aid with both illness prevention and treatment because IL-6 has been shown to contribute to the beginning of disease in animal models [66]. For example, IL-6 suppression decreased susceptibility to Castleman's illness and the cytokine storms brought on by chimeric antigen receptor (CAR) T-cell therapy. Investigations into the clinical etiology of the disease in critically ill COVID-19 patients revealed noticeably high levels of IL-6, and tocilizumab was proven to be beneficial in these patients [67]. It would seem advantageous to develop an IL-6 inhibitor with a short half-life that might be utilized to treat pathogen-induced cytokine storms, such as those brought on by sepsis, because infections are a severe side effect of using tocilizumab. This would be especially useful given to predict what is understood about these experiments [68]. Controlling IL-6 trans-signaling in endothelial cells is one way to prevent the spread of cytokine storms, which can be caused by conditions such as severe COVID-19 infections, severe burns, sepsis, and adverse drug reactions (ARDS). Additionally, the regulation of immunological responses is the responsibility of endothelial homeostasis [69,70]. When compared to other cytokines, IL-6 stands out due to its unique ability to regulate cell survival, proliferation, and differentiation. No other cytokine possesses this characteristic. It is also able to control both pro-inflammatory and anti-inflammatory responses in the cases of infections, autoimmune diseases, and cancer [71]. Interleukin-6 (IL-6) is a protein that has been shown to play a role in almost every facet of the innate immune system, according to the available evidence [7]. There is a possibility that this condition could lead to anemia, dysregulated lipid biosynthesis, and a variety of negative effects on the patients' well-being, including but not limited to depression, fatigue, pain, mood, and sleep [72,73]. The role that IL-6 plays in the functioning of hormones is directly related to all of these effects on the health of patients. This includes the behavior of the neuroendocrine system as well as homeostatic control of vascular function, insulin resistance, lipid metabolism, mitochondrial activities, and iron transport [74,75]. Its importance for regulating functional integration cannot be understated, in addition.

Table 1: Experimental and clinical evidence on the role of interference with IL-6 signaling as a potential preventive or therapeutic option for musculoskeletal disorders.

Author and Date	Study type	Drug and disease type	Outcome
Isaacs *et al*., (2013) [30]	Retrospective clinical study; data of 132 patients with RA	Tocilizumab *vs*. placebo; patients with RA.	The falls in CRP, hepcidin and haptoglobin levels in the first 2 wks correlated with a wk 12 rise in total iron-binding capacity and hemoglobin.
Genovese *et al*., (2015) [31]	Randomized clinical trial; 1197 patients with severe RA.	Sarilumab *vs*. placebo with MTX; Adults with moderate-to-severe RA and an inadequate response to MTX.	Sarilumab in combination with MTX provided sustained clinical efficacy (significant improvements in symptomatic, functional, and radiographic outcomes).
Khanna *et al*., (2022) [34]	Clinical trial on 107 patients with systemic sclerosis	Tocilizumab *vs*. placebo; patients with systemic sclerosis associated with interstitial lung disease.	Tocilizumab preserved lung function, slowing FVC decline in patients with SSc, including those with ILD. Long-term safety was consistent with the known safety profile of tocilizumab.
Dougados *et al*., (2013) [56]	Randomized double-blinded clinical trial on 556 patients with RA.	Tocilizumab; adults with active RA.	No clinically relevant superiority of TCZ+MTX add-on strategy over the switch to TCZ monotherapy was observed. The combination was more commonly associated with transaminase increases.
Gabay et al., (2013) [57]	Randomized clinical trial on 326 patients with active severe RA.	Tocilizumab *vs*. adalimumab; adults with severe RA for 6 months.	Tocilizumab was superior to adalimumab for reduction of signs and symptoms of RA in patients for whom MTX was inappropriate.
Burmester *et al*., (2016) [58]	Double-blind randomized controlled trial on 1162 MTX)-naive patients with early progressive RA.	Tocilizumab *vs*. placebo; patients with early progressive RA.	TCZ is effective in combination with MTX and as monotherapy for the treatment of patients with early RA.
Kaneko *et al*., (2015) [59]	Randomized, controlled study on 223 RA patients with moderate or high disease activity despite MTX treatment	Tocilizumab; RA patients with moderate or high disease activity.	Tocilizumab added to MTX more rapidly suppressed inflammation than tocilizumab switched from MTX
Genovese *et al*., (2014) [39]	Clinical trial in 221 RA patients.	Olokizumab *vs*. TCZ and TNF inhibitors; RA patients.	Olokizumab produced significantly greater reductions in DAS28(CRP) from baseline at Wk 12 compared with TNF inhibitors and TCZ.
Liu *et al*., (2022) [40]	Experimental animal study on Monkeys.	Humanized Anti-IL-6 antibody HZ0408b; animal model of collagen-induced arthritis.	HZ-0408b significantly ameliorated joint swelling after the onset of arthritis and reduced plasma CRP levels.
Kutsuna *et al*., (2022) [41]	Case study on 78-year-old Japanese woman with psoriatic arthritis.	Tocilizumab; Patient with psoriatic arthritis.	TCZ may address the unmet needs of patients with psoriatic arthritis who are resistant or intolerant to anti-TNF treatment.
Ravipati *et al*., (2022) [42]	Experimental study on mice; animal model of psoriatic arthritis.	Tofacitinib; Imiquimod-induced psoriatic arthritis in mice.	Tofacitinib, reduced psoriatic arthritis and epidermal STAT3 phosphorylation.
Valli et al., (2022) [43]	Clinical study on 6 patients with active RA resistant to MTX.	Tofacitinib; patients with active RA.	Tofacitinib downregulates several proinflammatory plasma proteins that may contribute to its clinical efficacy.
Latourte *et al*., (2017) [50]	Experimental animal study on mouse model of OA.	Anti-IL-6-R neutralising antibody MR16-1; mouse model of OA.	Systemic blockade of IL-6R alleviates destabilization of the medial meniscus-induced OA in mice.
Ko *et al*., (2022) [55]	Experimental animal study on collagenase-induced rat model of tendinopathy.	Substance P inhibitor; collagenase-induced rat model of tendinopathy.	Treatment with substance P inhibitor showed a normal tendon-like appearance with decreased IL-6 levels.

With a better knowledge of the processes underlying the IL-6 pathway, the ideal treatment for diseases linked to IL-6 may one day be discovered, as not all IL-6-associated disorders respond to drugs that inhibit IL-6 [76]. Research on biological DMARDs that interfere with the IL-6-IL-6R axis has undergone a period of substantial development over the course of the past ten years, making it one of the most rapidly growing areas of medical science. The findings of clinical studies on new medications like sarilumab, which target the IL-6 pathway in rheumatoid arthritis (RA) as well as other indications, are currently accessible. One of these indications includes different forms of arthritis [77]. Furthermore, the ineffectiveness of blocking the IL-6 pathway in the treatment of connective tissue diseases such as ankylosing spondylitis, psoriatic arthritis, or other disorders provided new insight into the immunopathology of these diseases [78,79]. However, there has been a huge rise in the amount of evidence supporting the use of tocilizumab and other biologic medicines in the treatment of RA in a range of diverse

groups [80-82]. Studies that investigated the potential advantages of decreasing or discontinuing IL-6 blockade medication in RA patients who have achieved clinical remission have provided clinicians with a number of useful insights [59,83,84]. Data on the safety of the medicine were gathered through clinical trials utilizing either tocilizumab or sarilumab, as well as a sizable prospective cohort examining the drug's long-term effects. Case studies indicate that tocilizumab, an anti-inflammatory drug, has been effective in treating people with polymyalgia rheumatica [85]. Tocilizumab was shown to have a steroid-sparing effect as well as clinical and serological improvement in patients with recent-onset polymyalgia rheumatica when it was used as a monotherapy. These findings were presented in two reports that were based on prospective, open-label phase II trials of tocilizumab. In the course of completing a review of the relevant literature, we came across these reports [86,87]. The outcomes of the phase III clinical trials involving tocilizumab and sarilumab have not yet been made public and are therefore unclear. This is due to the significant risk of bias that was present in both studies, as well as the absence of a comparator arm in one of the reports [60]. According to research that was conducted and published by Zhang *et al*. in 2020, tocilizumab has the potential to be proposed as an additional medication that is both safe and effective for the prevention of relapses in patients who have neuromyelitis optica spectrum disease (NMOSD). In comparison to azathioprine, they discovered that treatment with tocilizumab dramatically reduced the likelihood of a second episode of NMOSD [88]. After administering tocilizumab to individuals suffering from NMOSD, Yang *et al*. (2023) did not report any adverse effects or safety concerns. On the other hand, lengthy infusion intervals and high baseline plasma levels of glial fibrillary acidic protein may increase the chance of recurrence while tocilizumab therapy is being administered [89].

Conclusion

As was discussed in this article, data from experiments, translations, and epidemiological studies show that the IL-6 signaling pathway plays an essential part in the processes related to the pathogenesis and progression of a variety of musculoskeletal disorders. Some of these conditions include rheumatoid arthritis, osteoarthritis, tendinopathy, and spondylitis. Furthermore, recent data from randomized clinical trials and case reports provide evidence that targeting this pathway, at least through inhibition of IL-6R, significantly reduces the severity of illness event rates. This is of particular benefit to individuals who suffer from musculoskeletal disorders and have a residual risk of inflammation. In order to further our knowledge of inflammation and musculoskeletal disorders, the next step that we need to take is to test the downstream causal hypothesis, which states that targeting IL-6 itself can successfully and safely reduce progression event rates.

Conflict of interests

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Data sharing statement

N/A

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