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Evolving role of immunology in chronic pain medicine: tissue necrosis factor and interleukin modulatory treatments

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Abstract

Our immune system acts to protect us in times of stress and traumatic injury. As part of the immune response, the body produces various cytokines, which mediate or modulate immune functions. Such cytokines include tumor necrosis factor (TNF) and interleukin 6 (IL-6) and IL-17. These cytokines can also act on the nervous system to influence pain perception. TNF-α triggers an inflammatory response and two forms of programmed cell death, apoptosis and necroptosis, depending on the pathological state. For individuals with chronic conditions relating to immune deficiency, the actions of these cytokines can present as chronic pain states, significantly altering quality of life. One attractive potential solution for treating this immune linked pain is by altering signaling pathways of pain-enhancing cytokines. Infliximab and etanercept are TNF inhibitors that are currently on the market for use in the treatment of chronic pain. Secukinumab and tocilizumab serve as IL inhibitors, utilized for a similar purpose. These novel immunotherapies have shown efficacy in numerous clinical studies with acceptable side effect profiles. In this review, we summarize the pharmacological profiles of these drugs and discuss their usage in treating chronic pain.

Keywords

Cytokine modulation, chronic pain, TNF inhibitors, interleukin modulation, immunotherapy

Introduction

Pain is an age-old concern in patients which has challenged clinicians and scientists for centuries. The NIH has defined pain as "an unpleasant sensory and emotional experience", highlighting its subjective nature [1]. The biopsychosocial model of pain describes how pain is thought to be a product of genetics (biological), state of mind (psychological), and support systems (social) [1]. Given its undesirable effects, pain causes great distress for many individuals and in some cases, limits their ability to carry out day-to-day tasks.

Pain can be classified under three different umbrellas: acute pain, episodic pain, and chronic pain [1]. Chronic pain is a long-standing pathological state characterized by discomfort lasting more than three months [2]. Chronic pain has a large impact on the US population. A 2019 National Health Interview Survey (NHIS) found that the prevalence of chronic pain was 20.4% of the population, and that 7.4% of the population reported that their pain regularly limited daily activities [3].

Chronic pain can be classified into three subtypes: nociceptive, neuroplastic, and nociplastic [4]. Nociceptive pain is characterized by tissue damage, resulting in aching pain [3]. Neuropathic pain is a result of damage to nerves that transmit pain sensation, resulting in stabbing pain [3]. And finally, nociplastic pain arises from damages to the modulatory pain pathway without direct evidence of tissue or nerve damage [3]. All three types of pain may present with coexisting psychological distress [3]. Each form of pain has its own established treatment regimen, ranging from non-steroidal anti-inflammatory drugs, analgesics, muscle relaxants, and antidepressants to targeted interventional pain procedures [3].

When considering treatment options for pain, it is important to understand the molecular and physiological underpinnings of pain sensation. The nervous system plays a large role in transmitting pain sensation. When a noxious stimulus acts on peripheral nerve receptors, the peripheral nervous system carries that information up to the spinal cord and central nervous system, which then can act to reflexively remove the stimulus or integrate it into the brain's processing center [1, 5, 6]. Pain is also mediated or modulated by the endocrine system, which releases stress hormones following pain sensation by the nervous system [1, 7]. Finally, the immune system is also involved in pain signaling [1], and this system is the primary focus of the drugs introduced in this review.

The immune system is the body's natural form of defense against foreign pathogens or other insults and injuries. One of its defense strategies is inducing inflammation, where host cells release chemicals that indicate that the body has been breached [1, 8]. While this is a key mechanism by which our bodies fight off infection and insult, there are a few caveats that can lead to a diseased state. One caveat is in the case of autoimmune conditions, where the body recognizes "self" as "foreign", mounting an uncalled-for immune response [1]. Another caveat is when inflammation exceeds the appropriate duration of time or intensity [1]. The immune response is generally thought to occur in two different forms: innate immunity and adaptive immunity. Innate immunity is the standard, nonspecific response mounted by the body to any insult or pathogen, while adaptive immunity develops in response to specific pathogens or cells.

The innate immune system consists of physical barriers, defense cells, and proteins [8]. Following a breach of one of the innate immune system barriers, immune cells such as macrophages, epithelial cells, mast cells, and innate lymphoid cells release substances in the damaged area resulting in local inflammation [8, 9]. Host cell pattern recognition receptors (PRRs) attach to pathogen-associated molecular patterns (PAMPs) on the pathogen and damage-associated molecular patterns (DAMPs) released from damaged host cells and direct the removal of the pathogen and infected cells [9]. PRRs may also activate the complement cascade, which produces complement proteins, including C1–C9, and complexes that further enhances pathogen clearance [9]. PRRs can either be circulating or associated with cell membranes and intracellular signaling [9]. Examples of circulating PRRs include antimicrobial peptides, collectins, lectins, and pentraxins. Examples of cell-associated PRRs include toll-like receptors, nod-like receptors, and retinoic acid-inducible gene I-like receptors, among others [9]. Other immune cells called phagocytes are responsible for trapping pathogenic particles and alerting the adaptive immune system of their presence [8]. Examples of phagocytic cells include macrophages, monocytes, dendritic cells, neutrophils, and

eosinophils [9–12]. Cells called natural killer cells play a role as well, by identifying and destroying cells that may be hijacked by a pathogen [8]. Proteins like complement proteins and antibodies also contribute by either tagging pathogens for destruction or directly destroying them, or by recruiting other immune cells [8]. Acute phase reactants (APR) are proteins that are found in higher levels during inflammation [13]. Cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor (TNF)-α, and interferon γ induce the liver to produce changes in levels of APR [9]. APR levels can serve as a diagnostic clue for various conditions including rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, cardiovascular disease, infection, and malignancy [9].

The innate immune system also works closely with the adaptive immune system [9]. While the innate immune system is non-specific, the adaptive immune system acts to neutralize threats by directly targeting the pathogen in question through a learned response, resulting in a more effective clearance. In other words, cells of the adaptive immune system remember how to neutralize threats based on prior exposure. If the same threat is then reintroduced later, these cells activate and release substances that neutralize that specific threat, resulting in a more effective response than the innate immune system. The adaptive immune system primarily consists of cells called lymphocytes, which can be further classified as B cells or T cells [8]. These cells originate and mature in lymphoid organs, such as bone marrow and thymus, before migrating to peripheral lymph nodes and other secondary lymphoid organs for activation following encounters with foreign substances [14]. T cells and B cells have differing roles in the adaptive immune response. B cells are largely responsible for making antibodies, structures which neutralize pathogens or mark them for destruction [8]. Antibodies come in five flavors: IgG, IgA, IgM, IgE, and IgD. Each of these five types acts in unique circumstances. T cells further differentiate into specific types that have different roles in fighting off pathogens. T-helper cells are responsible for secreting substances that activate other immune cells [8]. On the other hand, cytotoxic T cells are responsible for binding to pathogen-infected cells and kickstarting their destruction [8]. Together, B and T cells help fight off pathogens in a coordinated fashion. As mentioned earlier, they also work with the innate immune system to mount a faster and more powerful immune response. For example, phagocytes of the innate immune system can act as antigen-presenting cells, which then interface with cytotoxic T cells to further mediate pathogen clearance [15]. B cells can also act as antigen-presenting cells.

Thus, T cells differentiate into various types, such as T helper cells and cytotoxic T cells, which each have unique roles in the adaptive immune response. T helper cells can then further differentiate into different subtypes. Examples of T helper cell subtypes include Th1, Th2, Th9, Th17, Th22, Tfh, Treg, iTreg, and Th3 cells [15]. Different T cell types are suited to different types of pathogens. For example, Th17 cells are involved in neutralizing extracellular pathogens such as bacteria and fungi [10]. The specific subtype which a T cell differentiates into depends on which cytokines it is exposed to. Continuing the example, when a T cell is exposed to IL-1 beta, IL-6, IL-21, and IL-23, it is induced to become a Th17 cell [10]. This new Th17 cell can then fight off extracellular pathogens by releasing various cytokines itself, such as IL-17 [10]. In turn, IL-17 will then activate other immune cells such as neutrophils to mitigate the damage [10].

In the present investigation, therefore, we focus on the TNF-α, IL-6, and IL-17 cytokines. TNF-α is released by Th1 cells and macrophages [10]. It acts to stimulate other T cells, such as formation of Th22, and induce other cytokines, metalloproteinases, and prostaglandins, as well as adhesion molecules to aid in immune cell recruitment [10]. Drugs that target TNF-α have been used to treat Crohn's disease, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis (pJIA), hidradenitis suppurative, and uveitis [10]. IL-6 is an interleukin cytokine produced by many different cell types, including Th2 cells [10]. It serves to induce B and T cell proliferation, as well as production of APR and natural protease inhibitors [10]. Drugs targeting IL-6 are used to treat Castleman disease, cytokine release syndrome, giant cell arteritis, rheumatoid arthritis, and systemic juvenile idiopathic arthritis [10]. Finally, as discussed above, IL-17 is an interleukin cytokine released by T cells and other lymphoid cells [10]. Drugs targeting IL-17 have been used to treat plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis [10].

TNF-α, IL-6, and IL-17

TNF modulators

TNF is a proinflammatory cytokine released by immune cells of both the natural and adaptive immune systems [16]. It can further be categorized into various subtypes (TNF-α, TNF-β, etc.). While TNF is also involved in development and circadian rhythm, here we primarily address its involvement in immunological defense. Specifically, TNF acts by inducing cell inflammation and death in pathways associated with pain [17]. Animal studies have found that TNF-α injections reproduce hypersensitivity symptoms like those in neuropathic pain [18, 19], and human nerve biopsies from pain patients show increased TNF-α expression [20], further substantiating its role in pain and inflammation.

Advancements in the field have allowed researchers to identify specific molecular mechanisms by which TNF carries out cell necrosis and apoptosis [17], allowing for targeted therapy options. One possible therapy involves downregulation of the TNF transmembrane receptor [21], which was found to reduce levels of TNF-α in rat models with neuropathic pain via a fusion protein [22]. Another mechanism of therapy is via TNF-α antagonists, which have also been found to lower pain in rat models [23, 24].

Infliximab and etanercept are two currently available drugs that block the signaling of TNF by binding to it [25, 26]. As of now, regulation on a systemic level has not proved beneficial in follow-up trials [27, 28]. Infliximab is given intravenously, while etanercept is given subcutaneously [25, 26]. Adalimumab, certolizumab pegol, and golimumab are other drugs that work similarly. All three can be administered subcutaneously, and golimumab can also be administered intravenously. All the TNF inhibitors presented here have been associated with adverse effects such as infection, rash, and gastrointestinal dysfunction, among others [25, 26, 29–31].

One study specifically investigated the use of certolizumab pegol in rheumatoid arthritis patients and found that pain scores significantly declined at each follow-up visit while on the medication [32]. Similarly, administration of sarilumab on top of methotrexate resulted in a greater decrease in pain scores for rheumatoid arthritis patients when compared to placebo [33].

Infliximab has also been evaluated for pain management in clinical trials in patients with disc herniation-induced sciatica. At regular follow-up for up to one year, Infliximab was found to significantly reduce leg pain when compared with saline [27].

IL modulators

ILs are another form of cytokine that can have either proinflammatory or anti-inflammatory effects by influencing the recruitment of immune cells and by damaging nervous tissue [34, 35]. Two such examples are IL-6 and IL-17, which regulate inflammation by engaging additional fibers and influencing the ion channels of nociceptors, resulting in greater sensitivity with a reduced threshold of activation [36, 37].

IL-17 is of particular importance, as it is involved with promoting secretion of IL-6 and other cytokines [38]. Animal studies have further demonstrated their effects. One study found reduced mechanical hypersensitivity and neuroinflammation, T cells, and macrophages at the site of injury following partial nerve ligation in IL-17 knockout mice when compared to controls [39]. Furthermore, IL-17 injections into mice knee joints were concurrent with enhanced nociceptor sensitization to stimuli and increased expression of IL-17R within dorsal root ganglia despite neutralization of TNF-α or IL-6, thus demonstrating its independent role in inflammation [40]. IL-6 has also been an evident inflammatory cytokine. Following sciatic nerve injury, rat models demonstrated a positive correlation between IL-6+ cells and the extent of allodynia [35, 41]. Moreover, knee joints and spinal cords in mice treated with IL-6 and IL-6R demonstrated hyperresponsive neurons upon mechanical stimulation [35, 42]. Increased IL-6 and IL-6R levels were also found in mice with intervertebral disc injury.

IL-17 serves as a prime target for immunotherapy when treating chronic pain. Secukinumab, a human monoclonal antibody, is one example of a drug targeting IL-17A, a subtype of IL-17. This drug is currently indicated for arthritic conditions such as psoriatic arthritis, ankylosing spondylosis, and rheumatoid

arthritis [38]. It has also been shown to reduce brain lesion activity on MRI in multiple sclerosis patients [43]. Ixekizumab is another antibody that works in a similar fashion. Finally, the antibody brodalumab has similar uses as the above drugs and may also be indicated for neuropathic pain [38]. While these drugs have not yet been evaluated on their effectiveness in chronic pain alone, they seem to modulate pain responses in chronic conditions and chemotherapy patients [38, 44].

Thus, IL-6 is a key cytokine that regulates immune response. Specifically, it increases production of APR and lymphocyte differentiation in response to inflammatory markers. It has been implicated in conditions such as rheumatoid arthritis, multiple sclerosis, cancer-related pain, and neuropathic pain [35, 45]. Similarly to IL-17, IL-6 serves as a target for immunotherapy. This is evidenced by one study which found that IL-6 inhibitors lowered proteins involved in pain signaling within the dorsal root ganglia [35, 46].

Drugs have also been developed that specifically antagonize IL-6 receptors, thereby altering the IL-6 signaling pathway. Such drugs include sarilumab and tocilizumab. Both can be given subcutaneously, and tocilizumab can also be given intravenously. Both drugs have adverse effects such as elevated serum alanine aminotransferase and aspartate aminotransferase. Sarilumab also poses the risk of infection, while tocilizumab may additionally have elevated serum cholesterol, constipation, infusion- and injection site-reactions [47, 48].

One study investigated the application of tocilizumab on spinal nerves for treatment of sciatica. The study found that after 4 weeks of use, patients treated with tocilizumab had significantly lower pain scores when compared to dexamethasone, and more patients treated with dexamethasone went on to have surgery than in the group treated with tocilizumab [49].

Therefore, IL-1 is another cytokine acting as an immune modulator. In this regard, the drug anakinra has been developed as an IL-1 receptor antagonist via subcutaneous administration. Adverse effects include rash, infection, and metabolic abnormalities [50].

Future directions

It is well documented that the immune response can be affected by different factors, both genetic and non-genetic, including age, gender, alcohol intake, obesity, and smoking. For example, aging leads to increased levels of IL-6 and unchanged levels of TNF-α, and men generally have higher levels of cytokine production [51]. In addition, acute alcohol intake decreases cytokine production [52], whereas chronic alcohol intake is associated with increased proinflammatory cytokine production, such as TNF-α and IL-6 [53]. Enhanced BMI and cigarette smoking are associated with enhanced levels of IL-6 and IL-18 [51, 54]. As a result of abnormal cytokine production and function in these conditions, immune modulation therapy may be affected.

In the future, the effects of alcohol, obesity, and smoking should be studied on cytokine modulators, including TNF-α, IL-6, and IL-17 modulating drugs. There have been some studies on the effects of obesity on etanercept, and a higher BMI is associated with lower serum etanercept concentrations [55]. The impact of chronic alcohol consumption and smoking on the efficacy of immune modulators are not well studied, and this could be a future direction to better control pain in patients.

Studying patients at the molecular level could also be a way to deliver more precise treatments to control pain. There are a number of genes that have been found by genome studies to be associated with increased incidences of pain, including variants within the *LDH1A2* gene that are associated with a severe osteoarthritis, variants in *TAOK3* that are associated with increased post-op pain, and a variant on 5p15.2 (upstream of TCP1-complex-5 gene and downstream of *FAM173B*) that is associated with a 30% higher risk for generalized chronic pain [56]. All of these genetic variants could be potential targets for pain management in patients identified as having one of these variants.

Genome-wide association studies can be done to look at potential reasons for differentiation in therapy response between individuals. For example, CD84 was found as a predictor of etanercept therapy in

rheumatoid arthritis; a better response to the drug was associated with higher CD84 expression [57]. However, this was not observed with infliximab or adalimumab, so one anti-TNF drug may work better than another in clinical practice. Tocilizumab was also found to provide lower disease activity and an improved disease activity score when patients had the *GALNT18* C-allele or the *CD69* A-allele [58].

Further research in genome-wide association studies could provide precision when deciding which immune-modulating drug could provide the most benefit and minimize side effect risks for patients. Comparing drugs in separate immune modulation categories (i.e., anti-TNF vs IL-6 vs IL-17) and genetic analysis of which variants have the best efficacy for each drug could provide an interesting approach to pain relief in patients.

Current applications and related research

While the concept of using TNF and interleukin modulatory treatments for chronic pain is relatively new, there are promising studies that demonstrate their relevance. One study that explored the use of Janus kinase (JAK) inhibitors in patients with inflammatory rheumatic diseases in relation to the management of fatigue describes the varying facets of fatigue in relation to stressors brought on by chronic pain states [59]. Biopsychosocial stressors can have a strong influence on the perception and presence of pain. Patients with chronic inflammatory diseases can be at risk of losing their job due to disability or having more negative environmental influences, leading to increased fatigue and worse pain management [59]. In addition to environmental stressors, the overproduction of cytokines (such as interleukins and TNF, for example) that activate JAK receptors in these conditions is also noted to contribute to initiating fatigue [59]. When managing rheumatoid arthritis, some anti-inflammatory interventions "including anti-TNF agents, rituximab, tocilizumab, canakinumab, abatacept, and anti-IFN-γ" reduced feelings of fatigue in patients suffering from rheumatoid arthritis when compared with placebo [60]. As such, it's important to note that targeting and inhibiting JAK receptors may present a solution to treating fatigue in addition to the chronic pain associated with inflammatory rheumatic diseases. Ultimately, these effects would help improve patient quality of life.

In addition to environmental stressors and the direct effects of inflammatory cytokine release, pain is also connected to the endocrine and nervous systems. Neuropathic pain happens as a result of a damaged portion of the nervous system. As 7–10% of the population is affected by neuropathic pain, the need for effective treatments is evident. One study explored the use of stigmasterol, a phytosterol commonly found in vegetable fats and plant oils [61], as a potential treatment for neuropathic pain [62]. Stigmasterol acts on various receptors involved in the inflammatory response, and more specifically has been found to act as an anti-inflammatory agent by inhibiting the IL-34/CSF1R signaling response involved in neuropathic pain in rat models [62]. The sequencing analysis from the rat models demonstrated that IL-34 is a major ligand for the CSF signaling pathway, as well as that the CSF1R pathway macrophages were increased in the setting of neuropathic pain [62]. Additionally, when cell groups were treated with stigmasterol, the concentration of IL-34 was found to be significantly reduced [62]. These findings demonstrate a successful example in rat models of how targeting receptors in the inflammatory response can provide a solution for a specific type of chronic pain. This further demonstrates the continuing need to explore targeted treatments in other types of chronic pain.

Conclusions

Pain is a subjective experience that manifests through the nervous system, the endocrine system, and the immune system. The immune system plays an especially large role and is a target for many drug therapies when treating chronic pain. As part of the immune response, in states of insult and injury, the body produces various cytokines such as TNF, IL-6, and IL-17 which regulate inflammation and pain perception. When excessively activated, these cytokines can result in states of chronic pain. Specific cytokine modulators are currently available and continue to be evaluated for their role in pain management. Of these modulators, different drugs have been shown to have differential success when treating specific conditions.

Abbreviations

APR: acute phase reactants

IL-6: interleukin 6

JAK: Janus kinase

PRRs: pattern recognition receptors

TNF: tumor necrosis factor

Declarations

Author contributions

RAK, ADK, DMP, AMH, GCW, ARR, SVH, SS, and GV: Conceptualization, Writing—original draft, Writing—review & editing. All authors listed have made a direct and intellectual contribution to the work.

Conflicts of interest

Giustino Varrassi is a Guest Editor of Exploration of Immunology, but he had no involvement in the decision-making or the review process of this manuscript. The other authors declare that they have no conflicts of interest.

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References

1. Pain [Internet]. Bethesda: National Institute of Neurological Disorders and Stroke; [cited 2024 Feb 22]. Available from: https://www.ninds.nih.gov/health-information/disorders/pain
2. Chronic Pain [Internet]. Cleveland: Cleveland Clinic; c2024 [cited 2024 Feb 21]. https://my.clevelandclinic.org/health/diseases/4798-chronic-pain
3. Chronic Pain and High-impact Chronic Pain Among U. S. Adults, 2019 [Internet]. CDC; [cited 2024 Feb 21]. https://www.cdc.gov/nchs/products/databriefs/db390.htm
4. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397:2082–97. [DOI] [PubMed]
5. Garland EL. Pain processing in the human nervous system: a selective review of nociceptive and biobehavioral pathways. Prim Care. 2012;39:561–71. [DOI] [PubMed] [PMC]
6. Brodal P. The Central Nervous System. 5th ed. Oxford University Press; 2010.

7. Tennant F. The physiologic effects of pain on the endocrine system. Pain Ther. 2013;2:75–86. [DOI] [PubMed] [PMC]
8. InformedHealth.org. In brief: The innate and adaptive immune systems. Cologne: Institute for Quality and Efficiency in Health Care (IQWiG); 2006.
9. An overview of the innate immune system [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://www.uptodate.com/contents/an-overview-of-the-innate-immune-system
10. Netea MG, van de Veerdonk FL, van der Meer JW. Primary immunodeficiencies of pattern recognition receptors. J Intern Med. 2012;272:517–27. [DOI] [PubMed]
11. Silva MT. When two is better than one: macrophages and neutrophils work in concert in innate immunity as complementary and cooperative partners of a myeloid phagocyte system. J Leukoc Biol. 2010;87:93–106. [DOI] [PubMed]
12. Serbina NV, Jia T, Hohl TM, Pamer EG. Monocyte-mediated defense against microbial pathogens. Annu Rev Immunol. 2008;26:421–52. [DOI] [PubMed] [PMC]
13. Acute phase reactants [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://www.uptodate.com/contents/acute-phase-reactants
14. Ruddle NH, Akirav EM. Secondary lymphoid organs: responding to genetic and environmental cues in ontogeny and the immune response. J Immunol. 2009;183:2205–12. [DOI] [PubMed] [PMC]
15. The adaptive cellular immune response: T cells and cytokines [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://www.uptodate.com/contents/the-adaptive-cellular-immune-response-t-cells-and-cytokines
16. Holbrook J, Lara-Reyna S, Jarosz-Griffiths H, McDermott M. Tumour necrosis factor signalling in health and disease. F1000Res. 2019;8:F1000 Faculty Rev–111. [DOI] [PubMed] [PMC]
17. Chu WM. Tumor necrosis factor. Cancer Lett. 2013;328:222–5. [DOI] [PubMed] [PMC]
18. Wagner R, Myers RR. Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. Neuroreport. 1996;7:2897–901. [DOI] [PubMed]
19. Sorkin LS, Doom CM. Epineurial application of TNF elicits an acute mechanical hyperalgesia in the awake rat. J Peripher Nerv Syst. 2000;5:96–100. [DOI] [PubMed]
20. Empl M, Renaud S, Erne B, Fuhr P, Straube A, Schaeren-Wiemers N, et al. TNF-alpha expression in painful and nonpainful neuropathies. Neurology. 2001;56:1371–7. [DOI] [PubMed]
21. Leung L, Cahill CM. TNF-alpha and neuropathic pain--a review. J Neuroinflammation. 2010;7:27. [DOI] [PubMed] [PMC]
22. Shamji MF, Jing L, Chen J, Hwang P, Ghodsizadeh O, Friedman AH, et al. Treatment of neuroinflammation by soluble tumor necrosis factor receptor Type II fused to a thermally responsive carrier. J Neurosurg Spine. 2008;9:221–8. [DOI] [PubMed] [PMC]
23. Sommer C, Lindenlaub T, Teuteberg P, Schäfers M, Hartung T, Toyka KV. Anti-TNF-neutralizing antibodies reduce pain-related behavior in two different mouse models of painful mononeuropathy. Brain Res. 2001;913:86–9. [DOI] [PubMed]
24. Svensson CI, Schäfers M, Jones TL, Powell H, Sorkin LS. Spinal blockade of TNF blocks spinal nerve ligation-induced increases in spinal P-p38. Neurosci Lett. 2005;379:209–13. [DOI] [PubMed]
25. Infliximab (including biosimilars): Drug information [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://www.medilib.ir/uptodate/show/8984
26. Etanercept (including biosimilars available in Canada): Drug information [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://www.medilib.ir/uptodate/show/8925
27. Korhonen T, Karppinen J, Malmivaara A, Autio R, Niinimäki J, Paimela L, et al. Efficacy of infliximab for disc herniation-induced sciatica: one-year follow-up. Spine (Phila Pa 1976). 2004;29:2115–9. [DOI] [PubMed]

28. Cohen SP, Wenzell D, Hurley RW, Kurihara C, Buckenmaier CC 3rd, Griffith S, et al. A double-blind, placebo-controlled, dose-response pilot study evaluating intradiscal etanercept in patients with chronic discogenic low back pain or lumbosacral radiculopathy. Anesthesiology. 2007;107:99–105. [DOI] [PubMed]
29. Adalimumab (including biosimilars): Drug information [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://www.medilib.ir/uptodate/show/8583
30. certolizumab pegol (Rx) [Internet]. WebMD LLC; c2024 [cited 2024 Feb 29]. Available from: https://reference.medscape.com/drug/cimzia-certolizumab-pegol-343185
31. Golimumab Injection [Internet]. American Society of Health-System Pharmacists, Inc.; [cited 2024 Feb 29]. Available from: https://medlineplus.gov/druginfo/meds/a610010.html
32. Bessette L, Haraoui B, Chow A, Fortin I, Dixit S, Khraishi M, et al. Effectiveness and safety of certolizumab pegol in rheumatoid arthritis patients in Canadian practice: 2-year results from the observational FαsT-CAN study. Ther Adv Musculoskelet Dis. 2019;11:1759720X19831151. [DOI] [PubMed] [PMC]
33. Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. Arthritis Rheumatol. 2015;67:1424–37. [DOI] [PubMed]
34. Justiz Vaillant AA, Qurie A. Interleukin. Treasure Island (FL): StatPearls Publishing; 2024.
35. Sebba A. Pain: A Review of Interleukin-6 and Its Roles in the Pain of Rheumatoid Arthritis. Open Access Rheumatol. 2021;13:31–43. [DOI] [PubMed] [PMC]
36. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018;281:8–27. [DOI] [PubMed] [PMC]
37. Totsch SK, Sorge RE. Immune System Involvement in Specific Pain Conditions. Mol Pain. 2017;13:1744806917724559. [DOI] [PubMed] [PMC]
38. Jiang X, Zhou R, Zhang Y, Zhu T, Li Q, Zhang W. Interleukin-17 as a potential therapeutic target for chronic pain. Front Immunol. 2022;13:999407. [DOI] [PubMed] [PMC]
39. Kim CF, Moalem-Taylor G. Interleukin-17 contributes to neuroinflammation and neuropathic pain following peripheral nerve injury in mice. J Pain. 2011;12:370–83. [DOI] [PubMed]
40. Richter F, Natura G, Ebbinghaus M, von Banchet GS, Hensellek S, König C, et al. Interleukin-17 sensitizes joint nociceptors to mechanical stimuli and contributes to arthritic pain through neuronal interleukin-17 receptors in rodents. Arthritis Rheum. 2012;64:4125–34. [DOI] [PubMed]
41. Cui JG, Holmin S, Mathiesen T, Meyerson BA, Linderoth B. Possible role of inflammatory mediators in tactile hypersensitivity in rat models of mononeuropathy. Pain. 2000;88:239–48. [DOI] [PubMed]
42. Vazquez E, Kahlenbach J, Segond von Banchet G, König C, Schaible HG, Ebersberger A. Spinal interleukin-6 is an amplifier of arthritic pain in the rat. Arthritis Rheum. 2012;64:2233–42. [DOI] [PubMed]
43. Havrdová E, Belova A, Goloborodko A, Tisserant A, Wright A, Wallstroem E, et al. Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study. J Neurol. 2016;263:1287–95. [DOI] [PubMed]
44. Luo H, Liu H, Zhang W, Matsuda M, Lv N, Chen G, et al. Interleukin-17 Regulates Neuron-Glial Communications, Synaptic Transmission, and Neuropathic Pain after Chemotherapy. Cell Rep. 2019;29:2384–97.e5. [DOI] [PubMed]
45. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2016;138:984–1010. [DOI] [PubMed]
46. Sainoh T, Orita S, Miyagi M, Sakuma Y, Yamauchi K, Suzuki M, et al. Interleukin-6 and interleukin-6 receptor expression, localization, and involvement in pain-sensing neuron activation in a mouse intervertebral disc injury model. J Orthop Res. 2015;33:1508–14. [DOI] [PubMed]

47. Sarilumab: Drug information [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://www.medilib.ir/uptodate/show/113355
48. Tocilizumab (including biosimilars): Drug information [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://www.medilib.ir/uptodate/show/10208
49. Ohtori S, Miyagi M, Eguchi Y, Inoue G, Orita S, Ochiai N, et al. Efficacy of epidural administration of anti-interleukin-6 receptor antibody onto spinal nerve for treatment of sciatica. Eur Spine J. 2012;21:2079–84. [DOI] [PubMed] [PMC]
50. Anakinra: Drug information [Internet]. UpToDate; c2024 [cited 2024 Feb 21]. Available from: https://medilib.ir/uptodate/show/9246
51. Horst RT, Jaeger M, Smeekens SP, Oosting M, Swertz MA, Li Y, et al. Host and Environmental Factors Influencing Individual Human Cytokine Responses. Cell. 2016;167:1111–24.e13. [DOI] [PubMed] [PMC]
52. Pruett SB, Zheng Q, Fan R, Matthews K, Schwab C. Ethanol suppresses cytokine responses induced through Toll-like receptors as well as innate resistance to Escherichia coli in a mouse model for binge drinking. Alcohol. 2004;33:147–55. [DOI] [PubMed]
53. Mandrekar P, Bala S, Catalano D, Kodys K, Szabo G. The opposite effects of acute and chronic alcohol on lipopolysaccharide-induced inflammation are linked to IRAK-M in human monocytes. J Immunol. 2009;183:1320–7. [DOI] [PubMed] [PMC]
54. Søegaard EGI, Kan Z, Aass HCD, Koirala R, Hauff E, Thapa SB. Abnormal Cytokines in Trauma Patients Explained by Obesity, Musculoskeletal Disease, Smoking, and Lung Disease. Neuropsychobiology. 2022;81:516–30. [DOI] [PubMed]
55. Balevic SJ, Becker ML, Gonzalez D, Funk RS. Low Etanercept Concentrations in Children With Obesity and Juvenile Idiopathic Arthritis. J Pediatr Pharmacol Ther. 2021;26:809–14. [DOI] [PubMed] [PMC]
56. Webster LR, Belfer I. Pharmacogenetics and Personalized Medicine in Pain Management. Clin Lab Med. 2016;36:493–506. [DOI] [PubMed]
57. Cui J, Stahl EA, Saevarsdottir S, Miceli C, Diogo D, Trynka G, et al. Genome-wide association study and gene expression analysis identifies CD84 as a predictor of response to etanercept therapy in rheumatoid arthritis. PLoS Genet. 2013;9:e1003394. [DOI] [PubMed] [PMC]
58. Maldonado-Montoro M, Cañadas-Garre M, González-Utrilla A, Plaza-Plaza JC, Calleja-Hernández MŸ. Genetic and clinical biomarkers of tocilizumab response in patients with rheumatoid arthritis. Pharmacol Res. 2016;111:264–71. [DOI] [PubMed]
59. Felis-Giemza A, Massalska M, Roszkowski L, Romanowska-Próchnicka K, Ciechomska M. Potential Mechanism of Fatigue Induction and Its Management by JAK Inhibitors in Inflammatory Rheumatic Diseases. J Inflamm Res. 2023;16:3949–65. [DOI] [PubMed] [PMC]
60. Almeida C, Choy EHS, Hewlett S, Kirwan JR, Cramp F, Chalder T, et al. Biologic interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev. 2016;2016:CD008334. [DOI] [PubMed] [PMC]
61. Bakrim S, Benkhaira N, Bourais I, Benali T, Lee L, Omari NE, et al. Health Benefits and Pharmacological Properties of Stigmasterol. Antioxidants (Basel). 2022;11:1912. [DOI] [PubMed] [PMC]
62. Si W, Chen Z, Bei J, Chang S, Zheng Y, Gao L, et al. Stigmasterol alleviates neuropathic pain by reducing Schwann cell-macrophage cascade in DRG by modulating IL-34/CSF1R. CNS Neurosci Ther. 2024;30:e14657. [DOI] [PubMed] [PMC]