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Drug-induced inflammation: A review of literature

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ABSTRACT

This review examines how various medications can trigger inflammation throughout the body. It explores causes, ranging from common pain relievers like NSAIDs to chemotherapy drugs. The review also highlights potential treatments, including established medications and promising new therapies. Physicians and patients can work together to reduce this risk by understanding these causes and implementing preventive measures, such as monitoring for side effects and using alternative medications when possible. Drug-induced inflammation can be categorized into four types based on the immune response involved. Symptoms vary by type and affected organ. Common symptoms include fever, malaise, joint pain, rash, and swelling. Diagnosis involves blood tests, imaging, and biopsies. Treatment primarily involves discontinuing the suspected drug and providing supportive care. The development of new drugs and therapies has made diagnosis challenging. However, recent advances in biomarkers and genetic risk assessment techniques are improving diagnosis and risk assessment of drug-induced liver injury. Preventive measures for drug-induced inflammation include monitoring for side effects, using alternative medications, developing new drug delivery methods, exploring new anti-inflammatory drugs, being aware of rare side effects, and understanding the underlying mechanisms.

Based on publications from the National Library of Medicine, this comprehensive review delves into the mechanisms by which various medications can instigate systemic inflammation. It scrutinizes the adverse effects of these drugs, encompassing complications such as pulmonary disorders, hepatic damage, and gastrointestinal injuries. The paper meticulously investigates therapeutic strategies, including the use of specific medications designed to mitigate the side effects of aspirin and shield the gastrointestinal tract from the impact of anti-inflammatory drugs. Furthermore, it explores innovative alternatives such as the application of bioengineered proteins to alleviate inflammation.

Drug-induced inflammation can be categorized into four types based on the type of immune response involved. Type I (IgE-mediated) reactions include symptoms such as urticaria (hives), angioedema (swelling), and anaphylaxis, and are diagnosed through skin prick tests and serum-specific IgE tests [1]. Type II (cytotoxic) reactions can cause hemolytic anemia, thrombocytopenia, and neutropenia, and are diagnosed using the direct Coombs test and blood smears [2]. Type III (immune complex) reactions manifest as serum sickness, vasculitis, and glomerulonephritis, and are diagnosed by checking complement levels and biopsying affected tissue [3]. Type IV (delayed, cell-mediated) reactions include contact dermatitis, drug rash with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome, and are diagnosed through patch tests and skin biopsies [4].

General symptoms of drug-induced inflammation include fever, malaise, joint pain, rash, and swelling. Specific symptoms vary depending on the affected organ or system. For example, drug-induced hepatitis presents with belly pain, jaundice, dark urine, and pale stools. Drug-induced lupus can cause fever, joint pain, muscle pain, pleuritic chest pain, and skin rash. Drug-induced myopathy leads to muscle weakness, myalgia, and rhabdomyolysis.

Diagnosis of drug-induced inflammation involves blood tests to detect inflammation markers, liver function tests, and complete blood counts. Imaging tests like MRI and CT scans can identify inflammation in organs or tissues, and biopsies of affected tissue can confirm inflammation and identify the cause. Detecting eye inflammation, such as uveitis, involves using a slit lamp microscope to examine the eye, tonometry to measure intraocular pressure, ophthalmoscopy to examine the back of the eye, OCT to map the retina and choroid, and angiography to photograph swollen blood vessels after dye injection.

To mitigate drug-induced inflammation, the primary treatment strategy is to discontinue the use of the suspected drug, which helps relieve symptoms [5]. Additionally, supportive care may include the use of alternative medications and treatments for the inflammation [5]. The development of various drugs and therapy methods has made diagnosing drug-induced inflammation challenging [6]. However, Clinton et al. have summarized the latest advances in the diagnosis and risk assessment of drug-induced liver injury [6]. Their work highlights new biomarkers and genetic risk assessment techniques [6].

Brzozowska et al. reported that aspirin, a common NSAID, inhibits COX-2 for therapeutic effects and COX-1, leading to gastrointestinal side effects [7]. Their study investigated aspirin's impact on the enteric nervous system (ENS), which regulates digestion. It was found that aspirin increased certain neurotransmitter expressions in the duodenum. These changes are likely due to the ENS adapting to inflammation caused by aspirin. Understanding this inflammation process and the role of the ENS could help develop new strategies for treating NSAID-induced lesions [7].

Alabdullah et al. addressed that lower urinary tract symptoms (LUTS) include overactive bladder and voiding disturbances [8]. LUTS can be caused by various factors, including drug-induced inflammation. Their paper presented a rare case of LUTS in a 12-year-old child, caused

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by scabies mites. This is the third such case reported in medical literature. Their study highlighted the need for further research into the causes of LUTS, including the role of infectious agents like scabies mites [8].

Xia et al. reported that 5-Fluorouracil (5-Fu) is a common drug for colorectal cancer treatment [9]. However, its long-term use can cause severe intestinal damage, including drug-induced inflammation. Their study found that Atorvastatincalcium can alleviate this damage and increase the sensitivity of 5-Fu to chemotherapy. Their combination therapy significantly reduced tumor growth in colorectal cancer cells, suggesting a novel therapeutic protocol for colorectal cancer [9].

Tadesse et al. assessed the impact of Adriamycin-Cytoxan (AC), a common chemotherapy treatment for breast cancer, on patients' hematological and electrolyte parameters [10]. They found that AC treatment significantly altered these parameters, potentially indicating drug-induced inflammation. Their study suggested the need for routine analysis of these parameters during treatment and further research into the drug's mechanism of action [10].

Daka et al. presented that intravitreal anti-VEGF therapy, often used for eye conditions, can cause a short-term increase in intraocular pressure (IOP) [11]. However, repeated injections can lead to a sustained IOP increase and secondary glaucoma, potentially due to drug-induced inflammation. High-risk patients, such as those with glaucoma or receiving frequent injections, require close monitoring and adjustable treatments to manage IOP. Early identification and prevention strategies are crucial to avoid sustained IOP elevation [11].

Cattaruzza et al. investigated and engineered precision-activated T-cell engagers (XPAT proteins) to enhance the therapeutic index [12]. These proteins target tumor antigens and were designed to be released by proteases in the tumor microenvironment, potentially reducing drug-induced inflammation. The HER2-XPAT protein demonstrated potent cytotoxicity and antitumor activity, with a strong safety margin in non-human primates. Their technology could be useful for tumor targets more widely expressed in healthy tissues [12].

Sharma et al. addressed that carbon dots (C-dots) have been studied for various applications, including bioimaging and antimicrobial activities [13]. Recently, the focus has shifted towards their anti-inflammatory properties, targeting biomarkers of chronic diseases. These C-dots have shown promising potential in combating inflammation-associated diseases, such as gout, liver diseases, and psoriasis, among others. Their effectiveness has been demonstrated in both in vivo and in vitro models, highlighting their potential as new anti-inflammatory drugs [13].

Wang et al. studied and examined the effects of methadone treatment on the brain's glymphatic system in opioid addicts in China [14]. Their results suggested that the treatment may aid in recovery from drug-induced inflammation. Their study also found a significant correlation between the glymphatic system and relapse rates, indicating its potential as a biomarker for relapse risk. This finding could lead to the development of new therapeutic strategies [14].

A 64-year-old woman with ulcerative colitis, treated with mesalamine, developed pericarditis, a rare but serious side effect [15]. Despite initial treatment and rheumatology follow-up, she had recurrent symptoms. Mesalamine-induced pericarditis was suspected, leading to discontinuation of the drug, resulting in complete resolution. Prompt recognition of this rare side effect is crucial to prevent progression and adverse outcomes. The association of inflammatory bowel disease with cardiac manifestations can complicate early diagnosis and treatment [15].

Diclofenac, an anti-inflammatory drug, can cause liver and kidney toxicity. A study on minipigs revealed that despite initial inflammation, diclofenac disrupts the liver's circadian rhythm, leading to hepatitis, glycogen depletion, and necrosis [16]. This disruption affected metabolic and immune responses, causing increased expression of pro-inflammatory agents and adrenocortical hypertrophy. The repression of REV-ERB, a link between the liver clock and glucocorticoid receptor, alleviated some immune responses. They suggested that diclofenac's hepatotoxicity is linked to liver clock desynchronization [16].

The literature review reveals that drug-induced inflammation can be attributed to several common causes, which can be categorized as follows:

1. Nonsteroidal Anti-inflammatory Drugs (NSAIDs): These pain relievers (e.g., aspirin) can inflame the gastrointestinal tract [7].
2. Chemotherapy drugs: Drugs like Adriamycin-Cytoxan (breast cancer) and 5-Fluorouracil (colorectal cancer) can damage tissues and trigger inflammation [9,10].
3. Antibiotics: In rare cases, antibiotics can cause inflammation in the lower urinary tract [8].
4. Ophthalmic medications: Intravitreal anti-VEGF drugs used for eye diseases can cause inflammation that leads to glaucoma [11].

The review results summarize preventive measures for drug-induced inflammation:

1. Monitor for side effects: Regularly check for changes in bloodwork, eye pressure, and other parameters depending on the medication [10,11].
2. Use alternative medications: Consider using medications with lower risks of inflammation, like Atorvastatincalcium with 5-Fluorouracil for colorectal cancer [9].
3. Develop new drug delivery methods: Targeted therapies like engineered T-cell engagers can reduce inflammation by precisely targeting diseased cells [12].
4. Explore new anti-inflammatory drugs: Research on carbon dots shows promise for treating chronic inflammatory diseases [13].
5. Be aware of rare side effects: Doctors and patients should be aware of less common side effects like mesalamine-induced pericarditis [15].
6. Understand the mechanisms: Studying how drugs like diclofenac disrupt the body's natural rhythms can inform future drug development to minimize inflammation [16].

By understanding these causes and implementing preventive measures, patients and doctors can work together to reduce the risk of drug-induced inflammation.

This in-depth review analyzed drug-induced inflammation, exploring its diverse causes (from common medications like NSAIDs to infections) and potential treatments (both established drugs and emerging therapies like engineered proteins). The results highlighted how some medications can trigger inflammation in various organs such as lungs and gut and discussed strategies to mitigate these side effects. The importance of monitoring potential side effects, like blood parameter changes and eye pressure increases, was emphasized. The review concluded by showcasing promising anti-inflammatory approaches, including novel materials like carbon dots. Overall, this review underlined the complexity of drug-induced inflammation and the ongoing research to manage and potentially prevent it.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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