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Shared Pathways, Divergent Outcomes: Understanding Autoimmune Hepatitis and Rheumatoid Arthritis Overlap

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Abstract

Background and Aim: Autoimmune hepatitis (AIH) and rheumatoid arthritis (RA) are distinct autoimmune diseases, yet their simultaneous occurrence, termed an overlap syndrome, poses significant diagnostic and therapeutic challenges. This literature review aims to synthesize current knowledge on AIH-RA overlap syndromes, focusing on shared autoantibody profiles, genetic predispositions, and clinical outcomes. The rarity of this specific overlap necessitates integrating findings from studies on broader autoimmune liver disease (AILD) overlap syndromes and AIH and RA individually to gain a comprehensive understanding.

Methods: A systematic review of the literature was conducted using relevant keywords (e.g., "autoimmune hepatitis," "rheumatoid arthritis," "overlap syndrome," "autoantibodies," "genetic predisposition," "HLA," "liver cirrhosis") in PubMed and other relevant databases. Studies focusing on AIH-RA overlap, AILD overlap syndromes, and individual AIH and RA characteristics were included. The quality of evidence was assessed based on study design and methodology. Data extraction included information on shared autoantibodies, HLA associations, clinical presentations, treatment responses, and disease progression.

Results: While AIH and RA have distinct autoantibody profiles – AIH is associated with ANA, SMA, and LKM-1, while RA involves RF and ACPA – overlap syndromes often exhibit a complex pattern of multiple autoantibodies, sometimes encompassing both liver-specific and rheumatic markers. This suggests shared immunological mechanisms. Genetic studies reveal that both AIH and RA have strong HLA associations; AIH is linked to HLA-DRB1*0301 and HLA-DRB1*0401, while RA is associated with the shared epitope (SE) in HLA-DRB1 alleles. However, the specific genetic basis of AIH-RA overlap remains largely unknown. Clinical outcomes are heterogeneous, with AIH manifestations (fatigue, jaundice, hepatomegaly) potentially coexisting with RA symptoms (joint pain, swelling). The combined presence of AIH and RA may lead to a more severe and rapidly progressive disease course, potentially increasing the risk of complications like liver cirrhosis and failure. Treatment responses to conventional therapies (corticosteroids, immunosuppressants) vary widely, highlighting the need for individualized treatment strategies.

Conclusion: The co-occurrence of AIH and RA represents a complex clinical entity with limited characterization. While shared autoantibodies and genetic predispositions suggest common immunological pathways, the precise mechanisms driving this overlap remain unclear. The available evidence suggests a potential association with more severe disease and variable treatment responses. Further large-scale studies are necessary to establish definitive diagnostic criteria, understand the underlying pathophysiology, and optimize treatment strategies for AIH-RA overlap syndromes. Collaborative efforts between hepatologists and rheumatologists are essential for improving the diagnosis, management, and overall outcomes for affected individuals.

Keywords: Autoimmune hepatitis, Rheumatoid arthritis, Overlap syndrome, Autoantibodies, Genetic predisposition, HLA, Liver cirrhosis

Introduction

Autoimmune diseases occur when the immune system mistakenly targets healthy tissue, disrupting the normal balance between immune defense and self-tolerance. These conditions can affect nearly every part of the body, often presenting with overlapping features that challenge diagnosis and treatment. A subset of these disorders, referred to as overlap syndromes, involves the coexistence of two or more autoimmune conditions in the same individual. These syndromes may reflect a shared immunological foundation, such as overactive T-cells, chronic inflammation, or the presence of specific autoantibodies. Autoimmune Hepatitis, or AIH, is a chronic liver condition characterized by immune-driven hepatic inflammation, and Rheumatoid Arthritis, or RA, is a systemic autoimmune disease that primarily targets the joints, and may represent one such overlap. Although they affect different organ systems, they are

both driven by immune dysregulation—raising questions about whether their intersection is coincidental or mechanistically linked [1].

Individually, AIH and RA have distinct clinical patterns. AIH tends to occur more frequently in women and often presents with elevated liver enzymes, fatigue, and sometimes jaundice. A definitive diagnosis usually involves a liver biopsy along with the detection of specific autoantibodies such as anti-smooth muscle antibodies. On the other hand, RA commonly emerges in middle age and manifests as persistent, symmetrical joint inflammation–typically involving the hands and wrists–along with systemic symptoms like low-grade fever and weight loss [2]. Despite their differences, AIH and RA share immunological hallmarks: both involve aberrant CD4+ T cell responses, elevated pro-inflammatory cytokines such as IL-6 and TNF-alpha, and associations with certain HLA-DR alleles. The overlap of these features may explain why some patients present with both conditions or develop one after the other. In some cases, liver abnormalities observed in RA patients are mistakenly attributed to drug toxicity or infection, potentially masking underlying AIH and delaying effective treatment [3].

The co-occurrence of these two diseases presents significant clinical challenges. From a diagnostic perspective, distinguishing drug-induced liver injury–especially in patients on methotrexate or biologics–from AIH can be difficult without biopsy confirmation. In terms of management, patients with RA and coexisting AIH often require careful coordination of immunosuppressive therapies that target systemic inflammation while minimizing hepatotoxicity. Failure to recognize the overlap may lead to suboptimal outcomes, either through under-treatment of liver disease or the unnecessary cessation of effective RA therapies [4]. Thus, identifying patients at risk for developing this overlap is critical–not only to guide personalized treatment decisions but also to understand how shared autoimmune mechanisms influence progression across different organ systems.

This paper aims to explore the intersection of AIH and RA with a focus on identifying shared pathogenic mechanisms and their clinical implications. Both diseases are driven by aberrant immune responses, yet the factors contributing to their co-occurrence remain poorly understood. A primary objective is to investigate overlapping immunological features, including dysregulated cytokine activity, T-cell dysfunction, and autoantibody production, to determine whether common pathways may explain their dual manifestation [5]. The detection of disease-specific autoantibodies, such as antinuclear antibodies and anti-smooth muscle antibodies in AIH, alongside rheumatoid factor and anti-cyclic citrullinated peptide antibodies in RA, suggests a potential convergence in humoral immune activity. Understanding these intersections could offer insight into whether overlap reflects a distinct clinical entity or a continuum of systemic autoimmunity.

In addition to immunological parallels, this study aims to examine whether shared genetic predispositions such as the presence of HLA-DR3 and HLA-DR4 alleles may increase susceptibility to both diseases. These associations could hold value in early screening and targeted prevention. Finally, this paper will assess how clinical presentation and outcomes in patients with AIH-RA overlap compare to those with isolated diagnoses. For instance, hepatic symptoms in RA patients are frequently misattributed to medication-induced liver injury, delaying proper diagnosis and increasing the risk of long-term hepatic damage. By identifying these diagnostic and therapeutic challenges, we aim to emphasize the need for integrating care models that accommodate the complexities of autoimmune overlap syndromes.

Methodology

A systematic literature search was conducted using PubMed, Web of Science, Embase, and Scopus. Search strategies combined Medical Subject Headings (MeSH) and keywords, including "autoimmune hepatitis," "rheumatoid arthritis," "overlap syndrome," "autoantibodies," "HLA," "liver cirrhosis," "treatment response," and "prognosis." Boolean operators (AND, OR, NOT) refined the search to enhance relevance and exclude non-pertinent studies. Studies were selected based on predefined criteria. Inclusion criteria encompassed observational studies (cohort, case-control, case series), systematic reviews, and meta-analyses focusing on adult AIH-RA patients. Randomized controlled trials (RCTs) were prioritized, though rare. Studies involving pediatric populations or other AILD-RA overlaps were included if relevant. Exclusion criteria included studies with unclear methodologies, single-case reports (unless providing unique insights), and those lacking sufficient data on shared autoantibody profiles, HLA associations, clinical presentations, treatment responses, disease progression, or survival rates. Non-English publications were excluded. Studies published from 1980 to present were considered to track advancements in understanding AIH-RA overlap. Only English-language studies were included.

A two-stage screening process was employed: first, title and abstract review to shortlist studies, followed by full-text assessment based on eligibility criteria. Data extraction included the use of a standardized form to ensure consistency, capturing study characteristics such as publication year, design, sample size, population, autoantibody profiles, HLA associations, clinical presentations, treatment regimens, disease progression, and outcomes. Extracted data were analyzed qualitatively to identify common themes, patterns, and discrepancies, considering methodological strengths and limitations. Findings were compared across studies to assess consistency regarding autoantibody profiles, HLA associations, clinical manifestations, and treatment responses. The methodological quality of studies was assessed using tools such as the Newcastle-Ottawa Scale for observational studies and the Cochrane risk of bias tool for RCTs. A narrative synthesis integrated key findings, highlighting areas of consensus, controversy, and knowledge gaps.

Results are structured into sections covering shared autoantibody profiles, genetic predispositions, clinical outcomes, research gaps, and future directions. Key limitations include language restrictions, potential omission of grey literature, methodological heterogeneity among included studies, and the rarity of AIH-RA overlap, necessitating integration of findings from related AILD conditions. This approach ensures a rigorous and comprehensive review of AIH-RA overlap syndromes, providing insights to inform future research and clinical practice.

Immunological Mechanisms and Shared Autoantibodies

Although autoantibody expression patterns in autoimmune hepatitis (AIH) and rheumatoid arthritis (RA) generally follow established diagnostic criteria, patients with coexisting AIH and RA may present with mixed serological profiles. In AIH type 1,

antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) are the most frequently detected markers, while liver/kidney microsomal antibody type 1 (LKM-1) is more commonly associated with AIH type 2 [6]. Soluble liver antigen/liver pancreas (SLA/LP) antibodies, identified more recently, are typically found in AIH type 1 patients who are negative for ANA and SMA and have been linked to more severe disease presentations [7]. In contrast, rheumatoid factor (RF) is primarily used for the early detection of RA, while anti-citrullinated peptide antibodies (ACPA) have become more prevalent as a specific and sensitive marker for RA diagnosis [8]. Although these autoantibodies are typically specific to each disease, some patients with overlapping AIH and RA may exhibit both hepatic and rheumatologic markers, suggesting shared or convergent immunological mechanisms. In a 2010 case-control study, Quintin et al. examined liver biopsies and autoantibody profiles in 41 RA patients on long-term low-dose methotrexate (MTX) therapy with elevated liver enzymes, comparing them to matched controls also on MTX but without enzyme abnormalities [9]. Rather than indicating direct MTX-induced hepatotoxicity, AIH-like lesions were found in the majority (52.5%) of patients, raising the possibility of underlying immune-mediated liver injury. Many of these patients tested positive for RA-specific autoantibodies such as RF and ACPA, yet were negative for traditional AIH markers like SMA and LKM-1. These findings underscore the diagnostic challenges in autoimmune overlap syndromes and highlight how rheumatoid arthritis may contribute to liver pathology that mimics autoimmune hepatitis through shared or parallel immunological pathways.

T-cell dysregulation, B-cell hyperactivity, common cytokine involvement, and molecular mimicry, which can lead to a loss of self-tolerance, have been identified as key contributors to the pathogenesis of both autoimmune hepatitis (AIH) and rheumatoid arthritis (RA). In a 2024 study by Talib et al., peripheral blood samples from healthy controls and RA patients were analyzed to investigate the role of T cells in B-cell differentiation [10]. Helper T cells from RA patients exhibited enhanced activation, which correlated with an increased frequency of B-cell differentiation. These findings suggest that constitutively active T cells in RA promote B-cell dysregulation and excessive autoantibody production, contributing to sustained immune activation. Similarly, in AIH, autoreactive T cells play a central role by secreting pro-inflammatory cytokines that stimulate B-cell activity and autoantibody production. In a 2017 study, Akberova et al. found significantly elevated serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in AIH patients compared to healthy controls, while interferon-gamma (IFN-γ) levels were notably reduced [11]. This cytokine profile, also observed in RA, supports the concept of overlapping immune dysregulation in both conditions. Moreover, both diseases have been epidemiologically associated with viral infections, such as Epstein-Barr virus (EBV), which may trigger autoimmunity in genetically susceptible individuals. This is because EBV proteins have been shown to share molecular similarities with self-antigens like collagen and keratin, potentially contributing to the activation of autoreactive T and B cells in RA [12]. Molecular mimicry promotes chronic inflammation in both AIH and RA, leading to sustained immune cell recruitment and the release of tissue-damaging enzymes. The parallel dysregulation of lymphocytes, elevation of pro-inflammatory cytokines, and shared mechanisms of molecular mimicry in both autoimmune hepatitis and rheumatoid arthritis highlight the potential for shared therapeutic targets, particularly in the context of overlapping immunopathogenesis.

Genetic Predispositions and HLA Associations

AIH and RA are associated with human leukocyte antigens (HLA) types suggesting a genetic link that predisposes people to develop these chronic diseases. AIH is primarily linked to Major Histocompatibility Complex (MHC) class II genes, specifically to the locus of HLA-DR [13]. These genes are underlying risk factors for many inflammatory and autoimmune diseases. AIH is presently linked to a primary susceptibility genotype of HLA-DRB1*0301* as well as a secondary genotype of HLA-DRB10401 [14]. More specifically, it is linked to position 71 in the HLA-DR beta chain which is encoded by the two susceptibility genotypes. These associations are important in pinpointing one of the many underlying factors of AIH. The susceptibility genes of HLA-DRB1*0301* and *HLA-DRB1*0401 have an association with Caucasian European and Northern American patients while other genes have been found for other ethnicity groups [15]. Similarly, RA holds an association with the HLA-DRB1 shared epitope (SE) linked to the same HLA-DR beta chain. The genes linked to RA have a common amino acid sequence in the part of the protein that binds to other molecules called the shared epitope [16]. This shared epitope is significant in understanding the pathogenetic autoimmune disease as they share motifs, permitting them to occur concomitantly.

The shared genetic markers between AIH and RA serve as a common risk factor for these conditions to occur simultaneously. There have been several links found in patients who have AIH and RA with the *HLA-DRB1*0401 posing a higher risk of concurrent autoimmune diseases [17]. This is prevalent in females especially those over sixty and with a history of autoimmune disease in their families [17]. The risk factors pose a unique challenge for patients whose symptoms may be masked and, in the difficulty, to diagnose both autoimmune diseases. This can also help physicians to understand the relationship between these chronic diseases and a better grasp on diagnosing them concurrently. Another important overlap is the general prevalence of another immune disease while 14%-44% of patients with AIH have another autoimmune disease [17]. Similarly, there is a 5% prevalence rate of RA in several autoimmune liver diseases including autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis [18]. This demonstrates the marked importance of recognizing genetic markers to further evaluate the treatment of a patient especially when the prevalence of other autoimmune disease is moderately high. Mihai et. al has also explored the link between RA and autoimmune liver diseases finding similar links with an Indian study finding a 5% prevalence of concurrent AIH and RA while a European study found the occurrence to be 1.8% [18]. These similar findings imply a link in genetic material causing AIH and RA to occur simultaneously in a patient.

Autoimmune diseases occur due to a myriad of risk factors other than HLA genetic susceptibility markers with non-HLA markers being a prominent factor. AIH is associated with genetic susceptibilities to cytotoxic T lymphocyte antigen-4 (CTLA-4), tumor necrosis factor- alpha (TNF-a), Fas, Vitamin D receptor, Signal transducer and activator transcription 4 (STAT-4), Transforming growth factor beta 1, Macrophage migration inhibitory factor, SH2B adaptor protein 3, caspase recruitment domain family member 10, and interleukin-23 (IL-23) [17]. This

exhaustive list generates a stronger ability to overlap between diseases. A similar prevalence of non-HLA genes has been found for RA which includes the protein tyrosine phosphatase 22 (PTPN22). This contains the variant Arg620Trp, creating a gene susceptibility for RA [19]. This specifically produces a lymphoid tyrosine phosphatase which helps to control T-cell signaling [19]. Dysfunction of this can hinder the ability of this gene and therefore create variants present in certain autoimmune conditions like RA. STAT-4 is another signal for RA and other chronic diseases such as Crohn's and celiac disease [19]. These known genetic factors contribute more to the specific diagnosis of autoimmune diseases and require further workup for definite diagnosing through the presence of overlapping HLA and non-HLA genetic factors.

Clinical Features and Disease Outcomes

AIH and RA overlap syndrome is characterized by a combination of liver-related and joint-related symptoms. On the hepatic side, patients often experience fatigue, jaundice, hepatomegaly, and an elevated risk of developing cirrhosis. Joint symptoms typically include polyarthritis, morning stiffness, and joint erosions [20; 21; 22]. The combination of these symptoms complicates diagnosis, making it essential to conduct a thorough clinical evaluation to effectively differentiate between individual conditions and the overlap syndrome.

The disease trajectory can vary significantly between isolated AIH and AIH-RA overlap syndrome. In cases where RA coexists with AIH, the disease course may become more severe, increasing the likelihood of progressive liver damage and cirrhosis. The coexistence of autoimmune conditions, such as RA, can complicate the prognosis and management of AIH [23]. In cases when autoimmune hepatitis coexists with other autoimmune disorders, patients typically experience more relapses and frequently require prolonged immunosuppressive therapy. As a result, healthcare providers must be vigilant in recognizing signs of worsening disease and ensuring that both the hepatic and rheumatologic components are adequately addressed.

Among patients with AIH-RA overlap, the risk of advancing to cirrhosis is notably higher compared to those with AIH alone. This heightened risk arises from the combined inflammatory stress and the potential for diagnostic delays [20; 21; 24]. Proactively identifying these patients and implementing close monitoring can help mitigate the progression of advanced liver disease.

Patients with AIH-RA overlap may also exhibit extrahepatic symptoms related to RA, such as rheumatoid nodules and vasculitis. These non-hepatic manifestations add another layer of complexity and require comprehensive management [25; 26]. Ensuring these manifestations are not overlooked is crucial for preventing further morbidity and optimizing patient outcomes.

Effectively managing patients with AIH-RA overlap requires a multidisciplinary approach integrating hepatology and rheumatology expertise. Comprehensive care plans should address both liver health and joint function, with early intervention critical to preventing severe disease progression and improving quality of life. As the understanding of AIH-RA overlap syndrome continues to evolve, further research will be essential to refine management strategies and optimize patient outcomes.

Treatment Strategies and Therapeutic Challenges

Responses to conventional therapies, such as corticosteroids and immunosuppressants, vary significantly, underscoring the need for personalized treatment approaches. Therapeutic strategies should be tailored to address the coexistence of hepatic autoimmunity and rheumatic manifestations observed in autoimmune hepatitis–rheumatoid arthritis overlap syndrome. In the majority of patients with AIH, an oral glucocorticoid (e.g., prednisone) serves as the cornerstone of initial therapy. The specific dosage is determined by factors such as symptom severity, serum aminotransferase and immunoglobulin G (IgG) levels, histologic findings, and risk of adverse effects. Typically, a low-dose prednisone regimen is initiated for two weeks as monotherapy, followed by the addition of an antimetabolite. To maintain therapeutic efficacy, an antimetabolite such as azathioprine (AZA) or, alternatively, mycophenolate is introduced. Most patients experience improvement in serum aminotransferase and IgG levels within four weeks of initiating glucocorticoid-based therapy. Immunosuppressive treatment should be continued for a minimum of two years after achieving biochemical remission before considering withdrawal.

Azathioprine is also used in the management of several rheumatic diseases, such as rheumatoid arthritis, suggesting its utility in minimizing polypharmacy in patients with AIH-RA overlap syndrome. However, AZA use is associated with adverse effects, particularly in the context of rheumatic conditions including gastrointestinal intolerance, bone marrow suppression, and infection. Although the incidence of toxicity is comparable to that of other conventional synthetic disease-modifying antirheumatic drugs (DMARDs) and mycophenolate mofetil, azathioprine should still be used cautiously in this population.

Tumor necrosis factor (TNF) antagonists, such as etanercept, have shown promise in improving histologic liver lesions associated with AIH in patients with RA [27]. This suggests potential benefit for patients with AIH-RA overlap syndrome. However, anti-TNF therapy has also been implicated in the induction of autoantibodies, such as antinuclear antibodies (ANAs) and anti-smooth muscle antibodies (ASMAs), leading to the development of anti-TNF-inhibitor-associated AIH (ATIAIH), thus limiting its therapeutic utility [28]. The paradox of biologic-induced autoimmune diseases complicates the use of TNF inhibitors in these cases. With the expanding use of biologic agents, a rise in the incidence and diversity of therapy-induced autoimmune disorders is anticipated. Paradoxically, treatment of these conditions may require re-administration of the same biologic agent implicated in their onset. In such cases, infliximab has been the most commonly used TNF-α inhibitor, particularly for RA-related indications. However, severe immune-mediated hepatic reactions have been documented with TNF-blocking agents—including infliximab, adalimumab, and etanercept—as outlined in a comprehensive review of 389 cases [29]. These findings highlight the complexity and potential for adverse drug interactions in managing autoimmune hepatitis-rheumatoid arthritis overlap syndrome.

Recent advances in immunologic research have introduced novel therapeutic agents targeting distinct pathways, presenting promising prospects for more precise and effective management strategies. For instance, a case report involving a patient with a rare tetrad of AIH, RA, Sjögren's syndrome, and type 1 renal tubular acidosis (RTA) demonstrated therapeutic benefit from Telitacicept. This agent is a dual inhibitor targeting the B

lymphocyte stimulator (BLyS) and A Proliferation-Inducing Ligand (APRIL) pathways. Telitacicept has shown promise in delivering meaningful efficacy with a favorable safety profile in patients with RA complicated by other refractory autoimmune disorders. However, limitations of this case include the absence of histopathological confirmation via liver biopsy and a relatively short duration of follow-up [30].

Ultimately, the management of autoimmune hepatitis-rheumatoid arthritis overlap syndrome necessitates a multidisciplinary approach that carefully balances the control of hepatic inflammation and articular manifestations while minimizing the risk of treatment-associated toxicity. Considering the complexity of this overlap syndrome, the development of individualized therapeutic strategies, tailored to each patient's clinical profile and comorbid conditions, is essential. Interdisciplinary collaboration between hepatology and rheumatology specialists in clinical practice can substantially enhance the management of these complex cases. Furthermore, large-scale investigations are essential to refine therapeutic strategies for autoimmune hepatitis-rheumatoid arthritis overlap syndrome.

Gaps in Knowledge and Future Directions

AIH and RA overlap remains under-researched, with limited large-scale epidemiological studies available to determine the true prevalence and risk factors. AIH is often associated with other autoimmune conditions, and up to 40% of AIH patients may have concurrent autoimmune diseases, including RA [31]. The reported prevalence of RA among AIH patients range from 1.6% to 5.4%, with higher rates seen in older populations, particularly those over 60 years old [31]. Despite this observed association, the extent to which RA and AIH share immunopathological mechanisms remains unclear, as many studies rely on small sample sizes.

Population-based studies in AIH patients suggest that rheumatologic symptoms may precede liver disease in a subset of individuals, further complicating early diagnosis [31]. In a study analyzing 278 patients diagnosed with AIH, 40% were diagnosed with another autoimmune condition, with 1.8% presenting with RA, highlighting the potential for systemic involvement [31]. However, these findings remain inconsistent across different cohorts due to variations in diagnostic criteria and study design. Expanding research efforts through longitudinal, multicenter studies could provide a clearer picture of the interplay between AIH and RA and help define optimal screening strategies for at-risk populations.

The identification of specific serological and genetic biomarkers remains a critical gap in understanding AIH-RA overlap. While HLA-DR4 has been identified as a susceptibility factor in both AIH and RA, its role in disease progression and severity remains poorly defined [32]. Other genetic markers that have been implied in the association of AIH and RA include PTPN22 and CTLA-4 gene polymorphisms but have not been well studied [33].

Beyond genetics, machine learning (ML) models are emerging as valuable tools for risk stratification in autoimmune diseases. A recent study demonstrated that ML-based predictive models incorporating ultrasound and serological markers improved the accuracy of RA relapse prediction [34]. These models employed XGBoost, which is highly effective in detecting complex, nonlinear relationships in biomedical data. By analyzing ultrasound parameters (e.g., synovial thickness, Doppler activity), cytokine levels, and patient demographics, the models identified subtle patterns linked to relapse that conventional statistical methods might overlook. To evaluate its performance, the study used the area under the curve (AUC) score, where XGBoost achieved an AUC of 0.747, outperforming traditional logistic regression which is limited by its assumption of linear relationships [34]. This suggests ML can capture more intricate disease patterns, allowing for more precise and individualized risk assessment in RA patients.

Clinically, these findings highlight the potential for ML integration into rheumatology workflows to predict high-risk relapse cases after treatment discontinuation. This could enable personalized treatment adjustments, reduce flares, and improve overall disease management. However, further validation in larger multi-center cohorts is needed before ML models can be fully implemented in practice.

The treatment of AIH-RA overlap presents a complex challenge due to the need for effective immunosuppression without exacerbating liver dysfunction. Standard AIH therapies, such as corticosteroids and azathioprine, can help control liver inflammation but may be insufficient in addressing joint disease in RA patients. Conversely, disease-modifying antirheumatic drugs (DMARDs) like methotrexate and leflunomide are commonly used in RA but carry a risk of hepatotoxicity, making them less favorable in AIH patients.

JAK inhibitors, including tofacitinib, baricitinib, upadacitinib, and filgotinib have shown promise in RA treatment and may offer new therapeutic avenues for AIH-RA patients. The JAK-STAT signaling pathway plays a key role in immune dysregulation in both RA and AIH, making JAK inhibitors a potentially effective treatment option for overlapping disease manifestations. A comparative analysis of these agents revealed no statistically significant difference in overall efficacy for RA patients, though tofacitinib showed a lower efficacy than upadacitinib in achieving disease remission [35]. However, concerns remain about the hepatic safety of JAK inhibitors. Studies suggest that JAK inhibitors, particularly tofacitinib, may elevate liver enzymes with a higher incidence of ALT/AST elevations in patients with preexisting liver disease. This raises concerns about their use in AIH patients with underlying hepatic impairment. Despite these risks, preliminary data suggest that selective JAK1 inhibitors, such as upadacitinib and filgotinib, may offer a safer alternative for AIH-RA patients due to their reduced off-target effects on JAK2 and JAK3 which are more closely linked to hematologic and hepatic adverse events [35]. Further studies evaluating the long-term safety of JAK inhibitors in AIH-RA patients are needed to determine their suitability in this population.

Another promising therapeutic avenue is interleukin-6 (IL-6) blockade, which has demonstrated efficacy in moderate-to-severe RA patients who do not respond adequately to conventional DMARDs. Tocilizumab, a monoclonal antibody that inhibits the IL-6 receptor, has been shown to significantly reduce Disease Activity Score (DAS28) and improve American College of Rheumatology (ACR) response rates compared to placebo [36]. In a randomized controlled trial, 59% of the patients receiving tocilizumab (8 mg/kg) achieved ACR20 responses at 24 weeks, compared to only 26% in the placebo group ($p < 0.0001$), demonstrating its effectiveness as an alternative therapy for RA [36]. Given IL-6's role in hepatic

acute phase response, blocking this cytokine may be beneficial in AIH-RA patients, though concerns remain regarding its impact on liver function [36].

Notably, tocilizumab therapy has been associated with elevations in hepatic aminotransferases, though these increases were often transient and did not lead to clinically significant liver disease [36]. However, patients with preexisting liver dysfunction were excluded from most clinical trials, making it difficult to assess the full risk profile of IL-6 blockade in AIH patients [36]. Given these uncertainties, further long-term studies are needed to determine the safety and efficacy of IL-6 inhibitors in AIH-RA overlap, particularly in patients with significant hepatic impairment.

Conclusion

AIH-RA overlap syndrome is a clinically significant convergence of autoimmune pathologies that challenges current diagnostic and therapeutic frameworks. This review highlights both the immunological and genetic intersections between AIH and RA, specifically in their complex autoantibody profiles and HLA associations. While shared markers suggest common underlying mechanisms, the genetic basis and pathophysiology of this overlap remains poorly defined. Clinically, the coexistence of hepatic and articular manifestations necessities a multidisciplinary diagnostic approach. Standard serologic and histologic criteria often fall short in distinguishing overlap syndromes, which may delay appropriate and timely intervention. Due to the potential for accelerated disease progression and increased risk of liver cirrhosis, timely recognition and tailored treatment strategies are essential. Conventional immunotherapies remain the primary management technique, but their variable efficacy further stresses the need for individualized treatment plans that weigh both hepatologic and rheumatologic considerations. Larger scale studies are needed to better understand the underlying pathophysiology and to establish definitive diagnostic criteria for AIH-RA overlap syndromes. Collaborative research efforts are critical to elucidate the immunologic mechanism of AIH-RA overlap and to develop effective evidence-based guidelines for diagnosis and treatment. As overlapping manifestations of autoimmune diseases become more frequently recognized and studied, coordinated effects between hepatology, rheumatology, and immunology will be key to advancing patient care and improving overall outcomes in these complex syndromes.

Conflict of Interest Statement

The authors of this manuscript declare that they have no conflicts of interest that are directly or indirectly related to the work submitted for publication. Specifically:

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