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A COMPREHENSIVE REVIEW OF IMMUNOMODULATORY DRUGS IN PREVENTING SECONDARY INFECTIONS IN IMMUNOCOMPROMISED PATIENTS: A NARRATIVE REVIEW

NARRATIVE REVIEW

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ABSTRACT

Background: Immunocompromised patients face heightened risks of secondary infections due to weakened immune defenses, often exacerbated by immunomodulatory drugs (IMDs). While IMDs are essential for managing conditions like cancer, autoimmune diseases, and transplant care, their use necessitates careful infection prevention strategies.

Objective; This review aims to synthesize current evidence on the mechanisms, benefits, and risks of IMDs, explore their integration with prophylactic strategies, and highlight emerging approaches for infection prevention.

Methods: A narrative review of recent literature was conducted, focusing on the roles of IMDs, associated infection risks, vaccination strategies, and novel approaches like trained immunity.

Findings: The findings emphasize the importance of personalized infection prevention, including pre-treatment vaccinations, tailored chemoprophylaxis, and immune monitoring. Emerging therapies, such as Toll-like receptor agonists, show potential for enhancing innate immunity. Despite advancements, challenges persist in balancing efficacy with infection risks, particularly during long-term IMD use.

Conclusion: Immunomodulatory drugs represent a dual-edged sword, requiring a multidisciplinary approach to optimize benefits and mitigate infection risks. Future research should address knowledge gaps related to long-term effects, optimal prophylactic strategies, and innovative immunomodulatory applications.

Keywords: Immunomodulatory Drugs, Secondary Infections, Immunocompromised Patients, Prophylaxis, Vaccination, Trained Immunity.

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INTRODUCTION

Immunocompromised patients, due to either inherent immune deficiencies or secondary causes such as chemotherapy, organ transplantation, or immunomodulatory treatments, face a heightened risk of secondary infections. These infections contribute significantly to morbidity and mortality, making their prevention a cornerstone of modern healthcare strategies. Immunomodulatory drugs (IMDs) have revolutionized the management of several diseases, including cancer, autoimmune disorders, and post-transplant care, by modulating the immune system to enhance host defenses or suppress pathological immune responses. However, the dual-edged nature of these therapies requires careful balancing of efficacy against potential infection risks. Secondary infections in immunocompromised patients are particularly challenging to address because of the complexity of their underlying conditions and the heterogeneity of pathogens involved. Such infections range from bacterial and fungal to viral and parasitic, often exacerbated by the broad-spectrum immunosuppressive effects of IMDs. For instance, biologics targeting specific immune pathways, such as TNF inhibitors or TLR agonists, have been associated with opportunistic infections, requiring tailored prophylactic measures(1-3).

Despite advancements in antimicrobial prophylaxis and vaccination, substantial gaps remain in our understanding of how best to integrate immunomodulatory drugs with strategies to prevent infections. Emerging research highlights the role of personalized approaches, including optimizing immunization protocols and using prophylactic agents, to mitigate infection risks without compromising therapeutic efficacy (4). The objectives of this review are multifaceted. First, it seeks to synthesize the current evidence on the effectiveness of various IMDs in preventing secondary infections in immunocompromised populations. Second, it aims to identify gaps in current practices and propose actionable recommendations for future research and clinical application. By offering a comprehensive overview of the interplay between immunomodulatory therapies and infection prevention strategies, this review aspires to guide clinicians in optimizing care for immunocompromised patients(5). The relevance of this review is underscored by the increasing prevalence of immunocompromised states due to advancements in medical treatments and aging populations. Additionally, the emergence of antimicrobial resistance and the global burden of infectious diseases further emphasize the critical need for nuanced approaches to managing secondary infections in these vulnerable populations (6). For example, Toll-like receptor (TLR) agonists show promise not only as immune boosters but also as vaccine adjuvants, illustrating the potential of leveraging innate immune pathways for enhanced infection control (7). Given the expanding role of IMDs in clinical practice, now is an opportune moment to evaluate their dual roles in therapy and infection prevention. This review will explore novel strategies such as immune reprogramming, the use of prophylactic antibiotics and antivirals, and innovative vaccine approaches to mitigate the risks of secondary infections. By synthesizing recent research and clinical guidelines, this review aims to provide a valuable resource for healthcare professionals navigating the complex landscape of immunomodulation and infection prevention(8).

BODY

Mechanisms of Immunomodulatory Drugs in Infection Prevention

IMDs operate by modulating the immune system, either by enhancing immune responses to combat pathogens or by suppressing immune activity to prevent autoimmunity. Certain IMDs, like Toll-like receptor (TLR) agonists, are known to activate trained immunity, reprogramming innate leukocytes to mount more robust responses upon subsequent exposures. This "trained immunity" enhances pathogen clearance and protects against secondary infections(7). Similarly, biologics targeting cytokines such as TNF inhibitors or IL-6 modulators can mitigate excessive inflammatory responses while preserving essential immune defenses(1).

Applications in Disease-Specific Contexts

Immunocompromised states arise from diverse conditions, such as malignancies, autoimmune diseases, and organ transplantation. In cancer, for example, multiple myeloma patients treated with immunomodulatory drugs like lenalidomide or pomalidomide exhibit improved survival but are at increased risk of severe infections. This necessitates prophylactic strategies, including antimicrobial therapy and adjunctive use of IVIG (intravenous immunoglobulin), to reduce infection rates(9). Similarly, autoimmune patients treated with TNF-blocking agents face elevated risks for opportunistic infections, highlighting the importance of tailored prophylaxis(4).

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Vaccination as a Complementary Strategy

The use of IMDs can impair vaccine efficacy, yet vaccination remains a cornerstone in preventing secondary infections. Evidence suggests that non-live vaccines, including those for influenza and pneumococcal diseases, are generally safe and effective in immunocompromised patients. However, their efficacy may be reduced during immunomodulatory therapy, necessitating timing optimization. Early vaccination before the initiation of therapy or booster doses may enhance immune responses in this population(4).

Challenges and Emerging Strategies

One of the major challenges in using IMDs is the balance between infection prevention and the risk of immunosuppression. For instance, high doses of corticosteroids or biologics targeting specific immune pathways can predispose patients to fungal infections like Pneumocystis jirovecii pneumonia. Prophylactic strategies, such as trimethoprim-sulfamethoxazole or atovaquone, are effective in high-risk patients (10). Newer approaches, such as the use of low-dose TLR agonists and cytokine modulators, show promise for reducing the infection burden while maintaining immune competence (7).

Integration of Prophylactic Measures

Prophylactic measures, including chemoprophylaxis, regular infection screening, and immune monitoring, are critical for infection control in this population. Studies recommend a multidisciplinary approach that combines IMD therapy with routine monitoring and infection-prevention protocols. For instance, combination strategies involving antimicrobial prophylaxis and preemptive therapies have been successful in transplant and cancer patients(6).

Early Insights into Immunomodulatory Therapies and Infection Risk

The initial era of IMDs, particularly in cancer and autoimmune disease management, brought substantial therapeutic advancements but also highlighted the unintended consequence of heightened susceptibility to infections. Early studies on thalidomide and lenalidomide in multiple myeloma revealed the risk of serious infections, including bacterial and fungal pathogens, during induction and maintenance therapy(9). This led to the development of prophylactic strategies, such as antimicrobial regimens and intravenous immunoglobulin (IVIG) therapy, to mitigate infection risks, especially during periods of profound immunosuppression(11).

The Role of Vaccination in Immunocompromised Populations

Vaccination emerged as a cornerstone in preventing secondary infections in immunocompromised patients. However, concerns over vaccine efficacy and safety in these populations, particularly for live vaccines, necessitated comprehensive studies. Recent evidence underscores the efficacy of inactivated vaccines, such as those for influenza and pneumococcal diseases, in patients undergoing IMD therapy (4). Importantly, vaccination before initiating therapy has been shown to improve immune responses and reduce infection rates, addressing earlier concerns about suboptimal immunogenicity during treatment(12).

Evolving Theories on Trained Immunity

One of the most exciting developments in recent years is the concept of "trained immunity," wherein innate immune cells are epigenetically reprogrammed to respond more robustly to infections. Toll-like receptor (TLR) agonists have been identified as promising agents for inducing this phenomenon, offering a novel approach to enhancing infection prevention without compromising the broader immune balance. This represents a shift from solely focusing on pathogen-specific interventions to leveraging the body's innate immunity for broad-spectrum infection control(7).

Emerging Strategies and Challenges in Risk Mitigation

Recent literature also highlights the importance of integrating multidisciplinary strategies to address the infection risks associated with IMDs. Studies emphasize the need for individualized risk assessments, combining chemoprophylaxis, vaccination, and regular immune monitoring to tailor prevention strategies (1). For example, prophylactic use of trimethoprim-sulfamethoxazole has proven effective in preventing Pneumocystis jirovecii pneumonia in high-risk patients, while atovaquone offers an alternative for those intolerant to standard regimens (10). However, challenges remain. The balance between infection prevention and maintaining therapeutic efficacy of IMDs continues to be a delicate task. For instance, while lenalidomide-based regimens have shown increased infection risks in multiple myeloma, their benefits in disease control often outweigh these concerns. This underscores the importance of closely monitoring patient profiles and adjusting therapeutic protocols as needed(9).

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Shifting Paradigms in Infection Prevention

The integration of new diagnostic tools, such as next-generation sequencing, has improved early detection and identification of pathogens in immunocompromised patients, facilitating timely interventions. Coupled with novel prophylactic agents and immune-boosting therapies, these advancements have significantly reduced infection-related morbidity and mortality. The focus is now shifting toward precision medicine approaches, where individual patient factors guide the choice of prophylactic and therapeutic measures(6).

Areas of Consensus

The literature broadly agrees on the effectiveness of certain prophylactic strategies in reducing infection risks in immunocompromised patients undergoing IMD therapy. For example, the use of trimethoprim-sulfamethoxazole to prevent Pneumocystis jirovecii pneumonia is widely accepted as a standard of care in high-risk patients, including those receiving biologics and corticosteroids (10). Additionally, there is consensus on the efficacy and safety of inactivated vaccines, such as influenza and pneumococcal vaccines, for mitigating secondary infections in immunocompromised populations, even though immunogenicity may be suboptimal during active therapy (4). Another area of agreement is the recognition of the immunosuppressive side effects of IMDs, such as increased risks of bacterial, fungal, and viral infections. Studies consistently report elevated risks of opportunistic infections in patients receiving TNF inhibitors, lenalidomide, or corticosteroid-based therapies(9).

Areas of Debate

Despite consensus on several points, debates persist regarding the optimal balance between IMD efficacy and infection risk. For example, while biologics targeting TNF-alpha or IL-6 are effective in autoimmune diseases like rheumatoid arthritis, their associated risks for tuberculosis and other latent infections remain controversial. Current literature calls for improved screening protocols but lacks universal guidelines for monitoring latent infections in patients on biologics (1). Additionally, the efficacy of live attenuated vaccines in certain immunocompromised subgroups remains contentious. While these vaccines are contraindicated for most immunocompromised patients, some argue they may be beneficial in select cases when administered before initiating IMD therapy. However, robust clinical evidence in this area is sparse, leading to divided opinions(4).

Gaps in Current Knowledge

Significant gaps exist in understanding the long-term impacts of IMDs on infection risk. For example, while short-term infection risks are well-documented, the cumulative effects of prolonged immunosuppression are less studied. This is particularly relevant for patients on maintenance therapies, such as lenalidomide for multiple myeloma, where the risk of secondary infections may increase over time (9). Another gap lies in the role of emerging immunotherapeutics, such as checkpoint inhibitors and TLR agonists, in infection prevention. While promising as immune boosters, their precise mechanisms, risks, and benefits in infection control remain underexplored (7). Similarly, there is a lack of consensus on whether to use prophylactic antibiotics universally or selectively based on patient profiles(13).

Emerging Trends

Recent advances in "trained immunity" are reshaping approaches to infection prevention. This phenomenon, driven by epigenetic reprogramming of innate immune cells, offers a promising avenue for enhancing immune responses to secondary infections. TLR agonists, for example, are being investigated as adjuvants to boost vaccine efficacy and as standalone immunotherapeutics (7). Additionally, personalized medicine is gaining traction as a strategy to mitigate infection risks. Advances in genomics and immune profiling are enabling tailored prophylactic and therapeutic regimens based on individual patient risk factors. For instance, predictive models using immune biomarkers are being developed to identify patients at the highest risk for severe infections, enabling earlier interventions(6).

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Table 1 Immunomodulatory Drugs Overview

Immunomodulatory Drug	Mechanism of Action	Key Infection Risk	Prevention Strategy
Lenalidomide	Inhibits angiogenesis and modulates cytokine production	Bacterial and fungal infections	Prophylactic antibiotics, IVIG therapy
TNF Inhibitors	Blocks tumor necrosis factor-alpha, reducing inflammation	Latent tuberculosis	Screening for latent TB, chemoprophylaxis
Toll-like Receptor (TLR) Agonists	Stimulates innate immunity and induces trained immunity	Potential overactivation of innate immunity	Further research needed

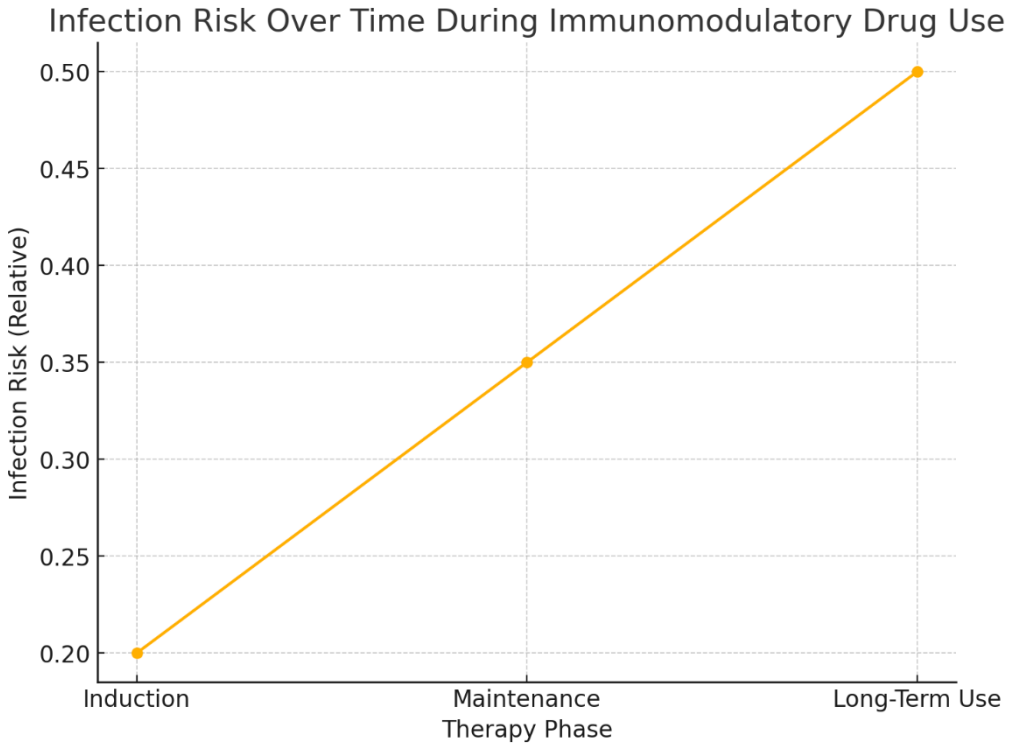

Figure 1 Infection Risk Over Time During Immunomodulatory Drug Use

DISCUSSION

This review aimed to explore the role of immunomodulatory drugs (IMDs) in preventing secondary infections among immunocompromised patients, integrating evidence on their mechanisms, effectiveness, and challenges. The findings confirm that IMDs, such as lenalidomide, TNF inhibitors, and Toll-like receptor (TLR) agonists, offer significant therapeutic benefits while simultaneously posing infection risks. These drugs modulate immune responses in ways that can either enhance pathogen clearance or inadvertently create vulnerabilities. Key findings highlighted the dual-edged nature of IMDs. For example, TNF inhibitors effectively manage autoimmune diseases but increase the risk of latent infections, such as tuberculosis, necessitating robust screening protocols (1). Similarly, lenalidomide and pomalidomide in multiple myeloma improve survival rates but carry heightened risks of bacterial and fungal infections during induction and maintenance therapy (9). This necessitates a multi-pronged approach combining prophylactic antibiotics, vaccination, and regular monitoring.

The role of vaccination emerged as a cornerstone in infection prevention, particularly in patients receiving biologics or corticosteroids. Evidence underscores the efficacy of non-live vaccines like influenza and pneumococcal vaccines, although their timing and immunogenicity remain critical factors for success(4). Meanwhile, emerging approaches like TLR agonists show promise in enhancing innate immunity, providing a new dimension to infection control (7). The findings of this review hold critical implications for the field. First, they emphasize the importance of individualized risk assessment in managing immunocompromised patients. By integrating immune profiling and patient-specific factors, clinicians can better tailor prophylactic strategies, minimizing risks while optimizing therapeutic outcomes. For example, pre-treatment vaccination and regular infection screening should become standard practices for patients initiating IMD therapy(13, 14). Second, the review highlights the untapped potential of trained immunity as a tool for infection prevention. TLR agonists and other immune-reprogramming agents could complement existing strategies, offering a broad-spectrum solution to infection risks. This represents a paradigm shift from pathogen-specific approaches to a more holistic enhancement of

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immune resilience (7). Additionally, this review contributes to existing literature by synthesizing findings across diverse contexts, from cancer to autoimmune diseases. It underscores the need for multidisciplinary collaboration in managing the complex interplay of IMDs and infection prevention, bridging gaps between oncology, immunology, and infectious diseases(15).

Despite its contributions, this review has several limitations. One key limitation is the potential bias in the selection of literature. While efforts were made to include recent and high-quality studies, the field is rapidly evolving, and some emerging evidence may not have been captured. For instance, the long-term impacts of new immunotherapeutics, such as checkpoint inhibitors, remain underexplored. Another limitation lies in the variability of study designs and populations. Many studies focus on specific patient groups, such as those with multiple myeloma or rheumatoid arthritis, making it challenging to generalize findings across all immunocompromised populations. Additionally, some studies rely on observational data, which may introduce confounding factors(16). The review also recognizes the lack of standardized protocols for integrating IMDs with infection prevention strategies. For example, while the role of chemoprophylaxis is well-established for certain infections, its broader application remains debated. Similarly, gaps in understanding the interactions between IMDs and vaccines limit the ability to provide universal recommendations. Finally, the rapid pace of advancements in immunology and infectious disease management means that some findings may become outdated as new therapies and prophylactic strategies emerge. This underscores the need for ongoing research and periodic updates to ensure that clinical practices align with the latest evidence.

CONCLUSION

This review highlights the dual roles of immunomodulatory drugs in providing therapeutic benefits while increasing susceptibility to secondary infections in immunocompromised patients. Key insights emphasize the importance of individualized infection prevention strategies, including timely vaccinations, prophylactic measures, and emerging concepts like trained immunity. While significant progress has been made, gaps remain in understanding long-term infection risks and the integration of novel immunotherapies. Future research should focus on personalized medicine approaches, optimizing the balance between drug efficacy and infection risk, and exploring innovative immunomodulatory strategies to enhance immune resilience, ultimately improving outcomes for this vulnerable population.

AUTHOR CONTRIBUTIONS

Author	Contribution
Sher Alam Khan*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Ayesha Usman	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Zahoor Islam	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Rida Fatima	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Irum Sajid	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
M. Abbas Sadiq	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Ayesha Saleem	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Ishfaq Aziz	Writing - Review & Editing, Assistance with Data Curation

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