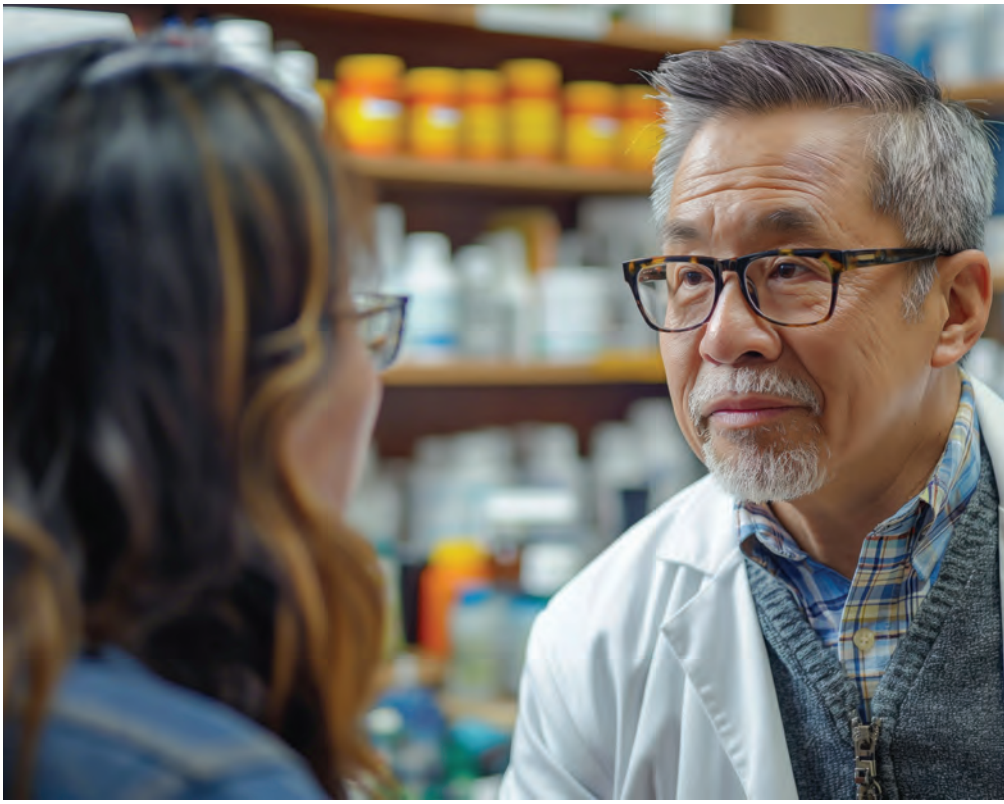
CHALLENGES IN IMiD PRESCRIPTION MANAGEMENT AND THE PHARMACIST'S ROLE



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The emergence of immunomodulatory drugs (IMiDs) — including lenalidomide, pomalidomide and thalidomide — has markedly transformed the therapeutic landscape for patients with multiple myeloma (MM), significantly improving clinical outcomes.

Lenalidomide is a cornerstone of front-line MM treatment, commonly administered in combination with proteasome inhibitors, corticosteroids and anti-CD38 monoclonal antibodies. Lenalidomide also plays a critical role in maintenance therapy following hematopoietic stem cell transplantation.

Conversely, pomalidomide is primarily utilized in the relapsed or refractory setting. Pomalidomide is considered after two previous lines of therapy including an IMiD (typically lenalidomide) and a proteasome inhibitor.

IMiDs remain integral to MM management, with patients often continuing therapy until disease progression.[1]

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Thalidomide, the first IMiD, was synthesized in the 1950s and initially marketed in Europe as an over-the-counter sedative and antiemetic for pregnant women, based on its perceived safety in mice models. However, its use was halted in the 1960s following the discovery of its teratogenic effects, which led to severe birth defects and embryo-fetal mortality. It was pulled from the market.[2]

When thalidomide was eventually approved by the U.S. Food and Drug Administration (FDA) in 1998, the FDA established the System for Thalidomide Education and Prescribing Safety (STEPS). The goal of STEPS was to control access to thalidomide, educate prescribers, pharmacists and patients on the risk of using thalidomide, and monitor compliance.[3] Ultimately, STEPS. became the THALOMID Risk Evaluation and Mitigation Strategy (REMS) program.

A REMS program was additionally established for lenalidomide and pomalidomide following their FDA approvals, citing the embryo-fetal toxicity risks.[4] The REMS program ensures that prescribers, patients and pharmacists are fully informed of the associated risks and adhere to stringent safety protocols.[5]

Presently, lenalidomide is utilized for not only MM but for conditions like lymphomas and myelodysplastic syndromes.[6]

Given the well-documented risk of embryo-fetal toxicity associated with many anticancer therapies, it is always imperative that a thorough and informed discussion regarding potential reproductive risks and the necessity of appropriate contraceptive measures be conducted between the patient and their oncologist prior to the initiation of treatment.[7]

This conversation should encompass

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both the short- and long-term implications of therapy on fertility and fetal development, ensuring that patients are fully aware of the precautions required to mitigate these risks.[8] These risks, however, are not unique to myeloma therapy and can add to the existing barriers of IMiD accessibility leading to treatment delays and patient dissatisfaction.

ACCESSIBILITY OF LENALIDOMIDE

Lenalidomide was approved by the FDA in 2005, but a generic version did not receive approval until 2022. The delay has been linked to approach of the drug manufacturer, Celgene, of filing multiple patents related to the drug, which may have discouraged competition and made it more difficult for other manufacturers to enter the market.[9,10]

An inquiry conducted by the House of Representatives Committee on Oversight and Reform reported that Celgene has raised the price of lenalidomide 22 times since its introduction in 2005.

According to the findings, these increases were primarily driven by financial incentives for executives and efforts to enhance shareholder value, rather than by additional research and development.[10] Furthermore, Celgene obtained patents for the RevAssist (REMS) program associated with lenalidomide, filing 22 patents and requiring its use for all purchasers. This approach has been viewed as a strategy to limit market competition.[11]

Through these measures, Celgene has sustained a leading position in the IMiD market for over a decade. This market dominance has enabled continued price increases, which have raised concerns about affordability and access to treatment for patients.[12] Ultimately, Celgene was acquired by Bristol-Myers Squibb (BMS) in 2019.[13]

Given that patients with MM may remain on IMiD therapy for extended periods, the REMS program can pose logistical challenges for prescribers and pharmacies. According to REMS requirements,

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prescribers must submit monthly surveys to obtain a valid authorization number which must be submitted to a REMS-certified specialty pharmacy.

These pharmacies are subject to strict dispensing criteria: Prescriptions must be limited to a 28-day supply, cannot include refills and may only be filled if the patient has seven or fewer days of medication remaining.

BMS is responsible for overseeing the REMS program for IMiDs and, as such, determines which specialty pharmacies are authorized to dispense these medications. These designated pharmacies are limited in number and are typically mail-order specialty pharmacies.[9]

For example, there are no REMS-certified pharmacies in Connecticut currently authorized to dispense lenalidomide. So, Connecticut resident-patients must receive lenalidomide from an out-of-state mail-order pharmacy. Notably, the Yale New Haven (YNH) Specialty Pharmacy has submitted multiple requests to become a REMS-certified dispensing pharmacy. All requests have been denied.

RESTRICTIONS TO DISPENSING

The REMS program for IMiDs imposes a stringent and arguably outdated set of requirements. These mandates apply not only to females of reproductive potential, but also to males and females who are not considered to be of reproductive potential.

Prior to every dispensation of an IMiD, all patients — regardless of reproductive status — must comply with REMS protocols. The most rigorous requirements are reserved for females of reproductive potential. These individuals must present a documented negative pregnancy test before each dispense of the medication.

Furthermore, the timing of the dispensation is tightly regulated: if the medication is not dispensed within seven days of the pregnancy test, the test is deemed expired, necessitating a repeat test before the drug can be released.[9] For patients of reproductive potential who are receiving maintenance therapy with an IMiD, provider visits may occur only every two to three months.

The requirement for monthly pregnancy tests introduces an additional layer of coordination between the physician's office and the patient. Patients can be asked invasive and repetitive questions by their provider's office, the pharmacy and the REMS program. This

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requirement, while rooted in safety concerns, may pose logistical and emotional burdens on patients and providers alike, and raises questions about the balance between regulatory requirements and clinical practicality. To address this issue in the myeloma clinic, implementing standing pregnancy lab orders allow patients the flexibility to visit any nearby draw station. Additionally, aligning pregnancy testing and medication refills with the patient's infusion schedule may enhance both convenience and continuity of care.

In addition to providers and pharmacists, patients also face unique challenges related to the REMS requirements. Patients must be enrolled in the REMS program and complete monthly surveys and counseling sessions. These counseling sessions for females include using two effective birth control methods, not sharing lenalidomide pills and not donating blood. In addition to not sharing lenalidomide and donating blood, males must not donate sperm and must use a condom.

This coordination can often cause delays. As previously mentioned, females of reproductive potential must fulfill these requirements in addition to providing a negative pregnancy test within seven days prior to each dispensation.

Furthermore, because one of the dispensing requirements is a supply limited to 28 days or less, patients who need an extended supply for travel must coordinate this request with BMS REMS, their insurance provider and the dispensing pharmacy no more than one week prior to their departure date.[9] If IMiD doses are held or adjusted due to side effects, a partial fill or prescription change may require a new REMS authorization number as well.

IMiD prescriptions can be difficult to access due to high costs and multiple administrative requirements, which may lead to delays in filling prescriptions.

In 2020, lenalidomide was the third largest revenue-producing pharmaceutical product worldwide, with $12.2 billion in sales.[14]

The REMS program for IMiD therapy presents distinct barriers and challenges that affect both patients with MM and their care team. The involvement of the pharmacist can enhance the efficiency of IMiD initiation, continuation and monitoring, while also facilitating communication between oncology teams and specialty pharmacies.

In addition to insurance often dictating which specialty pharmacy patients must use, medications frequently require prior authorizations and come with high copays. One retrospective analysis found that IMiD prescriptions averaged $227.23 prior to financial assistance and $80.11 after financial assistance, highlighting the high costs associated with this medication.[15]

Additionally, a retrospective analysis from Brown University Health showed that lenalidomide prescriptions took a median of eight days to fill, with those requiring financial assistance experiencing longer delays.[16]

Despite the healthcare team's best efforts, it is not uncommon for patients to experience delays in receiving their IMiD supply before starting accompanying infusion treatments. Financial constraints, along with complex prescription requirements, can contribute to these delays and impact timely access to care.

To help alleviate the financial burden associated with IMiD medications, pharmacists can proactively support the prior authorization process early in the treatment course. At Yale New Haven Health (YNHH), a dedicated financial team manages prior authorizations, while the Medication Assistance Program team offers additional support to patients facing financial hardship. Furthermore, many specialty pharmacies provide their own financial assistance programs, expanding the resources available to patients in need.

PHARMACIST'S ROLE

To alleviate the administrative burden on physicians and nursing staff — particularly in high-volume cancer centers — some institutions have adopted pharmacist-led models to manage REMS compliance and patient follow-up.

At Fred Hutchinson Cancer Center (FHCC) in Seattle, pharmacists oversee IMiD prescription appropriateness, provide patient education and follow-up, and fulfill REMS regulatory requirements. Prior to this model, the care team spent an average of 240 hours per month on IMiD-related regulatory tasks. The integration of pharmacists into this workflow yielded positive outcomes for both patients and providers.[17]

A similar approach has been implemented at the University of Illinois Chicago. Pharmacists at the University of Illinois Cancer Center assist with REMS enrollment and IMiD prescription management. The presence of an on-site oncology specialty pharmacy with IMID-dispensing capabilities further streamlines the process, allowing patients to conveniently access their medications.

Additionally, at cancer centers where a collaborative practice agreement exists, pharmacists can fully prescribe, where permitted by state law and institutional policy, IMiDs and maintain ownership of these prescriptions.[18]

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Institutions that have successfully adopted these models typically designate a dedicated clinical pharmacist within the myeloma clinic. However, barriers to implementation may arise in settings where pharmacists have competing responsibilities, such as infusion order verification, operational duties or additional clinical duties. FHCC addressed this challenge by hiring a project coordinator (medical assistant) to support pharmacists with the administrative aspects of IMiD care coordination.[17]

While pharmacist-led IMiD initiatives can support providers and nurses in alleviating the burden of prescribing and managing these therapies, the administrative responsibilities associated with such programs fall outside the typical scope of practice for a clinical oncology pharmacist.

YNHH treats patients with MM across several sites throughout Connecticut. At the satellite locations, IMiD management is typically handled by practice nurses, as the volume of IMiD prescriptions is relatively low.

In contrast, at the main myeloma clinic — where prescription volume is significantly higher — the process is primarily pharmacist-driven. While the practice nurse is responsible for initially enrolling the patient, the hematology clinical pharmacist oversees monthly refills and ensures compliance with REMS requirements. The team includes two myeloma clinic pharmacists who rotate between inpatient and outpatient responsibilities, meaning only one pharmacist is on-site in the clinic at any given time.

Within the myeloma clinic, pharmacists manage over 250 IMiD prescriptions. In addition to REMS-related tasks, the myeloma clinic pharmacist is also responsible for verifying infusion clinic orders, conducting patient workups, providing counseling, assisting with treatment plan modifications and addressing drug information inquiries. Pharmacists also coordinate with the authorization team to facilitate copay issues if patients report needing financial assistance.

Since the YNH specialty pharmacy does not have REMS-dispensing authorities, the clinic relies on insurance to determine which pharmacy patients must use. Working with numerous mail-order specialty pharmacies across the country does not allow the provider offices to build the same rapport with a single pharmacy as the team is able with non-IMiD oral anticancer therapies at the YNH specialty pharmacy.

This can become problematic when there are issues with a prescription and the pharmacy team is unable to determine its exact location within the dispensing process; especially when it becomes lost among the numerous mail-order pharmacies.

Despite these challenges, the healthcare team continues to refine the processes to streamline workflow and improve patient satisfaction.

FUTURE DIRECTIONS

As IMiDs continue to be a foundational component of MM therapy, pharmacists serve as invaluable members of the interdisciplinary care team. As the role of the pharmacist continues to evolve and expand within oncology care, there is growing hope that cancer centers will be able to designate clinical oncology pharmacists to manage IMiD refills under collaborative practice agreements.

Such agreements would empower pharmacists to prescribe refills independently, operating under the oversight of a licensed provider while adhering to established protocols. In addition, these collaborative agreements could authorize pharmacists to make evidence-based adjustments to IMiD dosing in response to treatment-related toxicities.

Pharmacists would also be able to prescribe supportive care therapies aimed at mitigating adverse events, thereby enhancing patient safety and improving treatment adherence. This expanded scope would not only streamline care delivery but also alleviate the administrative burden on physicians, advanced practice providers and nurses. It would allow for a more efficient and patient-centered approach to managing complex oncology regimens.[17,18]

This process could offer additional benefits given the continually evolving landscape of myeloma therapy and the anticipated introduction of two new IMiDs currently in development.[19]

CONCLUSION

The REMS program for IMiD therapy presents distinct barriers and challenges that affect both patients with MM and their care team. The involvement of the pharmacist can enhance the efficiency of IMiD initiation, continuation and monitoring, while also facilitating communication between oncology teams and specialty pharmacies.

Moreover, the pharmacist plays a pivotal role in minimizing delays, enhancing treatment adherence, and safeguarding against interruptions in care. Nonetheless, clinic structures and pharmacist workloads remain potential obstacles to broader adoption of this model.

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