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Biologic Injections with Prolonged Action: Transforming Immune System Therapies

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ABSTRACT

Long-acting injectable (LAI) biologics, composed of a biologically active pharmaceutical ingredient (API) combined with polymers that form microparticles, suspensions, or hydrogels, have recently emerged as a promising and transformative approach in immunopharmacology. These LAIs function as controlled-release drug delivery systems, administered parenterally into deep or lateral muscle tissue or subcutaneous fat. Following administration, the polymers gradually degrade, allowing the API to be released steadily within a therapeutic window lasting from several weeks to months. Compared with daily oral dosing, LAIs offer multiple advantages, including improved patient adherence, stabilized plasma drug levels with fewer peaks, reduced human error, and applicability in various psychophysical disorders. In recent years, significant investment by the biotechnology sector in biologic drug development has driven the increasing incorporation of biologic APIs and excipients in nanoformulations for novel LAI products. This next-generation class of LAIs may modify pharmacokinetics and injection site reactions, thereby influencing the histological and immunohistochemical characteristics of the long-lasting depot formed at the injection site. Consequently, a detailed evaluation of LAI formulations is crucial. Given the novelty and complexity of these therapies, assessing potential risks and implementing pre-market management strategies is essential. This review, therefore, provides a systematic evaluation of the toxicological and inflammatory responses associated with therapeutic LAI formulations in both rodent and non-rodent experimental models.

Keywords: Administration, Bulk drugs, Polymers, Hydrogels, Drug delivery systems, Rodentia

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Introduction

The pharmacologic effects of biologic agents often deviate from initial expectations. This is partly due to the fundamental differences between biologics and small-molecule drugs. More importantly, the wide interindividual variability in response to therapy—from lack of efficacy to adverse effects—frequently limits the applicability of population-based models. The rapid advancement of pharmacogenomics (PGx) offers the potential to integrate individual genetic profiles into clinical decision-making, potentially improving patient outcomes. Evidence suggests that pharmacogenomic factors contribute to the variability in responses to therapeutic monoclonal antibodies (mAbs) in certain indications [1]. However, knowledge of these determinants remains incomplete and not universally applicable, and as a result, translational PGx trials have not fully met expectations.

The efficacy of biologics varies both in magnitude and duration across individuals. Some patients are observed to be either primary or secondary nonresponders [2], often attributed to underdosing or accelerated clearance mediated by antidrug antibodies (ADAs). In general, the interindividual variability in clinical outcomes frequently surpasses the variability in drug exposure and correlates poorly with it [3]. This indicates that multiple disease- and therapy-related factors contribute to drug action, with plasma drug levels representing only one aspect. A substantial portion of patients receiving mAb therapy do not achieve adequate responses [4-6]. Factors affecting variability include pharmacokinetic (PK) and pharmacodynamic (PD) differences. While differences in drug

clearance, target antigen expression, and clinical status can influence PD responses, the role of inflammation in reducing mAb activity has not been fully explored [7].

TNF-blocking mAbs are commonly employed in the treatment of rheumatoid arthritis (RA) and Crohn's disease (CD). Despite therapeutic advances, a significant proportion of patients fail to respond to mAb therapy initially (primary nonresponders) or eventually lose their response over time (secondary nonresponders) [8].

Overview of biologics in immunopharmacology

Biologics now account for over 30% of approved pharmaceuticals and have substantially expanded therapeutic options, including enzymes, antibodies, proteins, antisense molecules, glycoproteins, and oligonucleotides. Recent biologics largely comprise monoclonal antibodies and cytokines conjugated with polyethylene glycol to prolong their half-lives. Many of these are immunomodulatory agents—such as growth hormones, globulins, insulin, platelet-derived products, sterile ophthalmic ointments, cytokine-based therapies, and nucleosides—and can be categorized based on their mechanism of action: cytokine immunomodulators, receptor-blocking immunomodulators, and other signaling modulators [9].

The U.S. Food and Drug Administration (FDA) has recently provided guidance for the development of long-acting injectable biologics and approved agents such as adalimumab, darbepoetin alfa, glatiramer acetate, olanzapine pamoate, paliperidone palmitate, risperidone, and interferon beta-1a for monotherapy use. Frequently used long-acting biologics include nucleoside or co-receptor inhibitors, IL-1 inhibitors, α1-proteinase inhibitors, calcium-calcineurin modulators, and hematopoietic agents. Given the growing interest in these therapies, this review highlights the challenges in developing safer immunomodulatory biologics and offers funding and strategic recommendations to minimize off-target effects [10, 11].

Need for long-acting formulations

Injectable therapies have been employed for centuries and remain one of the most widely used administration routes in contemporary medicine. Currently, small-molecule drugs dominate nearly 90% of the global pharmaceutical market and continue to lead in new drug approvals. However, many small-molecule agents require multiple daily doses due to their short biological half-lives. This frequent dosing can lead to substantial fluctuations in plasma drug concentrations and an increased risk of adverse effects [12]. Consequently, patient adherence is often limited, with nearly 50% failing to follow prescribed regimens. Over the next decade, the use of immediate-release formulations is projected to decline by approximately 10%, largely due to adherence challenges affecting hundreds of millions of patients [13].

Several drugs, particularly those targeting chronic conditions, have achieved—or are poised to achieve—blockbuster status, which may increase the number of required injections and prolong therapy duration. Targeted small molecules, however, often exhibit limited specificity, reducing therapeutic efficacy and causing off-target effects. Bulk drugs (BDs) are developed not only to extend the duration of treatment but also to build upon existing therapies. As adjuncts in managing a wide array of diseases, BDs are increasingly being tailored toward personalized and patient-specific approaches [14].

Biologics in immunopharmacology

Biologics now constitute over 30% of approved pharmaceutical products and have greatly expanded therapeutic options across a variety of diseases, including immune-mediated inflammatory disorders (IMIDs) and cancers. Approximately one-third of these biologics are immunomodulatory agents [15]. Based on their mechanism of action, immunomodulatory biologics can be classified into three categories: Type I, cytokine immunomodulators that mimic, replace, or enhance endogenous cytokines [16]; Type II, antibody-based activators that bind specific targets and stimulate immune cell signaling; and Type III, blocking immunomodulators that bind immune-related targets and inhibit their activity. Due to their high target specificity, these biologics theoretically minimize off-target effects [17].

Mechanism of action

Immunopharmacology examines how drugs influence the immune system. Small molecules such as cyclosporine are used to suppress immune responses during transplantation, while corticosteroids are employed to treat inflammation, cancer, and autoimmune diseases. Over recent decades, biologics—complex proteins and macromolecules such as monoclonal antibodies, fusion proteins, and vaccines—have emerged as precise

therapeutic tools. These agents can selectively target leukocyte surface proteins that small molecules cannot. Future developments in immunopharmacology are expected to leverage biologics with precise spatiotemporal control, alongside applications of systems and synthetic biology to design personalized therapies [15, 18, 19].

Types of biologics

Biotherapeutics represent a diverse subset of biologics, and their complexity historically made the development of long-acting injectable or orally repurposed formulations challenging. Current prototypes are generally designed for infusion or small-volume subcutaneous injection, with ongoing research exploring site-specific intramuscular delivery. By contrast, small molecules have long been available in conventional intramuscular or subcutaneous formulations. After intramuscular administration, the drug forms a depot in the muscle, releasing gradually into systemic circulation and producing prolonged absorption and sustained pharmacokinetic profiles. Protein-based biologics are increasingly important for treating chronic conditions, including cancer, immune-mediated disorders, inflammatory diseases, and rare genetic conditions [20].

Biotherapeutics are produced using recombinant DNA or hybridoma technologies and include monoclonal antibodies, cytokines, growth factors, hormones, and regulatory peptides. They exhibit a wide range of molecular weights and partition coefficients. For instance, Fab fragments are low-molecular-weight biologics with low octanol/water partition coefficients, whereas complete or partial IgG antibodies are approximately ten times larger, with correspondingly higher partition coefficients. This diversity allows biologics to target molecules across a spectrum inaccessible to small-molecule drugs. Notably, over half of the top 50 best-selling biologics in 2017 had molecular weights exceeding 90 kDa, while small-molecule drugs generally favor low molecular weight and low partition coefficients. Biologics also exhibit greater chemical heterogeneity, presenting development challenges, as variations in chemical and physical properties can significantly impact potency, pharmacokinetics, and stability. Vesicular carriers are often required for biologic transport. Insulin was the first biologic introduced as a therapeutic in 1982, necessitating innovative delivery methods, such as battery-powered medical devices. By 2020, only one competitor remained in the clinical development pipeline [21].

Challenges in biologics administration

Biologic therapies have emerged as highly effective treatments for various cancers and chronic conditions, demonstrating notable efficacy in clinical trials over the past decade. These agents are generally selective for disease-related targets and exhibit minimal toxicity at therapeutic doses. Monoclonal antibodies (mAbs) represent a major class of biologics and one of the fastest-growing segments of the pharmaceutical industry [22]. However, efforts to develop orally administered biologics have largely been abandoned due to rapid degradation by gastrointestinal proteases and poor absorption from the gastrointestinal tract [23]. As a result, parenteral administration remains the primary route for biologics. Patient adherence to biologic therapy is critical for optimal outcomes, prompting ongoing research into strategies that enhance adherence [24].

The first mAb approved for cancer therapy was rituximab in 1997, followed by adalimumab for chronic inflammatory diseases in 1998. Advances in target selection, antibody engineering, and manufacturing technologies fueled the rapid expansion of mAb development, making mAbs the largest class of approved biologics. Today, mAbs targeting a wide spectrum of disease pathologies dominate the late-stage clinical pipeline, accounting for over half of global biologic sales [5, 25].

Patient adherence and compliance

Despite the growing importance of biologics in disease management, non-adherence and non-compliance remain significant challenges. Studies estimate that approximately 60% of all prescription medications are not taken exactly as prescribed, with adherence rates for injectable biologics dropping as low as 16%. The reasons for non-adherence are multifactorial, though evidence points to patient-related factors such as lack of confidence, engagement, or investment in their treatment. To address these issues, many patient support programs (PSPs) for biologic injectables have been developed, often incorporating devices that facilitate medication administration [26, 27].

The design and functionality of the administration device significantly influence patient choice, adherence, and compliance. Research highlights the variability in patient preferences, indicating that no single self-injection device can meet the needs of all patient populations. Providing healthcare professionals (HCPs) with options to select suitable devices for individual patients can enhance personalized support, increase engagement, and

improve clinical outcomes. Broad implementation of such a choice across the EU could empower patients, improve treatment experiences, enhance adherence, and reduce both the economic and societal burden of disease [27].

Injection site reactions

Injection site reactions (ISRs) following subcutaneous administration of biologics remain poorly characterized in the literature. Data on ISRs are only available for a limited number of trials, and detailed ISR information for individual biologics is often lacking. Given that subcutaneous injections deposit biologics into soft tissue, which may provoke local irritation and immune responses, patient concerns regarding ISRs could negatively affect adherence and the wider acceptance of subcutaneously delivered biologics. Reported prevalence of ISRs for established biologics ranges from 6.7% to 60.7%, but cumulative ISR rates across biologics have not been systematically calculated due to insufficient data. Understanding the relationship between ISRs, treatment adherence, and therapeutic response is essential, as these reactions may represent an underappreciated and undervalued category of adverse events in subcutaneous biologic therapy [28].

Advantages of long-acting injectable biologics

Improved patient convenience

With the rising prevalence of chronic diseases, biological disease-modifying antirheumatic drugs (bDMARDs) have emerged as a major advancement in pharmacotherapy. By targeting specific components of the immune system, biologics allow for improved long-term disease management, reduce functional impairment, and enhance patients' quality of life. They have consistently shown superior efficacy compared with conventional disease-modifying antirheumatic drugs (DMARDs) in maintaining health and preventing joint damage. Common biologics used in rheumatology include agents targeting tumor necrosis factor (TNF), interleukin-6 and its receptors, CD20, T-cells, and other recently identified molecular targets.

Long-acting biologics provide novel delivery routes and broaden therapeutic options. Traditional anti-TNF biologic therapy for chronic inflammatory conditions typically requires weekly or biweekly subcutaneous injections. Despite their proven effectiveness, challenges related to frequent subcutaneous administration persist. Depot formulations of biologics, which can be administered monthly, bi-monthly, or even less frequently, represent a paradigm shift in immunopharmacology. Although most long-acting biologics are evaluated for specific indications rather than immunopharmacology as a field, their eventual adoption is expected to significantly reshape treatment approaches for chronic inflammatory diseases. The introduction of a long-acting anti-TNF biosimilar could serve as a benchmark in this evolution. While pharmaceutical and immunological hurdles remain, advances in manufacturing and clinical research are paving the way for this new paradigm. Additionally, innovative biomedical devices enabling optimized administration schedules may enhance patient experience and commercial success [28].

Enhanced efficacy and safety profiles

Long-acting injectable (LAI) biologics have the potential to transform immunopharmacology. These formulations allow for controlled systemic delivery of both small- and large-molecule therapeutics, gradually releasing encapsulated drugs over time. Compared to conventional oral therapies, LAIs offer multiple benefits, including improved adherence, depot administration, and the ability to tailor dosing and release kinetics to optimize therapeutic outcomes [29]. Importantly, encapsulation enhances the stability of biologics in systemic circulation [30]. Beyond these advantages, LAIs also improve the delivery efficiency of therapeutic proteins, particularly in immunosuppressive agents. Several agents, including cyclosporine A, methotrexate, novel TNF-α inhibitors, leflunomide, and tacrolimus, have demonstrated promising results, supporting LAIs as effective treatments for a range of immune-related disorders [28, 31].

Formulation technologies for long-acting injectables

Injectable therapeutics have become a cornerstone of modern medicine and are expected to play a central role in future drug administration strategies. Current long-acting formulations often rely on small-molecule chemical entities to create depot injections in solution or crystalline form. These formulations aim to produce sustained drug release and favorable bioavailability. However, frequent dosing can still increase the risk of drug–drug interactions.

The use of nanoscale delivery systems—including nanoparticles, micelles, and nanosuspensions—is gaining increasing attention [32]. Despite their potential, high-solid drug deposition in subcutaneous or muscle tissue carries risks such as necrosis or granuloma formation. Various inorganic and organic nanoparticles, excluding liposomes and lipocrons, are being evaluated for their long-acting potential. The performance of these formulations depends heavily on excipient properties, with factors such as supersaturation and crystallization points critically influencing drug release. Supersaturation can cause early precipitation due to low solubility, while variations in crystallization points can reduce precipitation efficiency. Local blood flow governs drug release into systemic circulation, and drug concentrations at the injection site can peak sooner than anticipated. Without proper redistribution, drugs may enter the liquid–vapor phase prematurely, potentially reducing bioavailability [33].

Polymer-based systems

Long-acting injectable therapeutics represent a transformative approach in medicine, with the potential to change how treatments are administered. Biocompatible polymers delivered via intradermal or subcutaneous routes can be taken up by immune cells, effectively mimicking natural infection processes and potentially eliminating the need for external adjuvants. Agarose scaffolds, which resemble the water content and pore structure of soft tissue, have been studied to assess immune cell interactions. In a meta-in-vitro analysis, SH rods were internalized by mast cells, macrophages, and neutrophils, while fibroblasts showed no uptake. Notably, macrophages and mast cells degrade agarose more slowly than fibroblasts [34]. Cutting-edge imaging and analytical techniques, such as FIB-SEM, EDX, cubem3, and TIRE, have enhanced the detection of these rod-like structures within biologically relevant samples, allowing precise quantification inside cells. These findings shed light on how different immune cells process polymeric materials and inform the evaluation of safety risks associated with polymer degradation. Furthermore, this knowledge may guide the design of more efficient in vivo testing systems by targeting the immune cell populations that actively internalize SH rods [35].

Advanced liposomal formulations

The development of long-acting biologics has expanded rapidly, particularly agents targeting inflammatory signaling pathways, cytokines, or their receptors, with promising applications in oncology and other disease [36]. Modern drug delivery platforms, including liposomes, microparticles, and nanoparticles, have enhanced pharmacokinetics and enabled new administration strategies [37]. Subcutaneous and intravenous depot formulations can slowly release drugs over time, offering a controlled delivery mechanism. Some strategies involve conjugating inert polymer chains to active molecules to form large hydrophobic complexes that circulate slowly and gradually reach target tissues. Other approaches include in situ gelation of semisolid foams or implants for prolonged release [37]. Nevertheless, conventional solubility-enhancing excipients may provoke local adverse reactions, including severe inflammation or granuloma formation. Recent innovations combining nanoparticles with supramolecular matrices have yielded injectable suspensions that are more stable and safer, representing a promising direction for future long-acting therapies [35, 38].

Clinical potential of long-acting biologics

Long-acting biologics are capable of sustained therapeutic effects, spanning several weeks or months following administration. Their broader clinical adoption could redefine treatment strategies for many severe or chronic diseases. Ongoing research is investigating how these formulations influence tissue response and drug delivery at a cellular level [39]. Rabbit models have been used to study granuloma formation after subcutaneous administration of model biologic particles. By applying automated microparticle detection algorithms, researchers can quantify primary, amorphous microparticles with high precision, even in samples initially considered particle-free [34]. Traditional methods measure tissue response via cross-sectional area, but combining these models with refined injection techniques, automated histology, and statistical analysis enhances both speed and objectivity in evaluating local tissue reactions [35].

Chronic inflammatory diseases

Over the past decade, long-acting injectable biologics (LAIBs) have seen remarkable progress, with development accelerating even more rapidly since the COVID-19 pandemic. Efforts have focused on creating new delivery platforms, reformulating existing therapies, and exploring novel therapeutic applications. Among the various emerging technologies, liposomal carriers, ohmic-insulated systems, and injectable hydrogels have been

investigated. Despite these advances, significant technological challenges remain. Long-acting approaches involving protein–drug conjugates and gene editing are still in their infancy. Notably, non-invasive delivery methods—including inhalation, oral routes, ophthalmic, nasal, or sublingual administration—offer substantial promise for future biologic therapies [5, 40].

Currently, LAIBs are available globally, and discussions have centered on their potential to transform treatment strategies, particularly in developing countries and resource-limited settings. Healthcare infrastructure in middle- and low-income regions often struggles to support the administration of systemic biologics, and treatment adherence for chronic conditions such as rheumatoid arthritis, psoriasis, and ankylosing spondylitis remains suboptimal. Large cohort analyses of patients initiating conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) provide insight into these challenges [41].

Oncology

Biologic therapies are widely used in oncology for a range of cancers, as well as in chronic inflammatory disorders like arthritis, inflammatory bowel disease, and psoriasis. With many monoclonal antibodies (mAbs) losing patent protection, there is growing interest in biosimilars as a strategy to reduce costs. A notable trend is the preference for subcutaneous (SC) over intravenous (IV) administration of biologics, particularly when cost and convenience are comparable. Patients often perceive SC administration as giving them greater control, reducing hospital visits and procedural stress, and allowing more time for personal or social activities [42-44]. Expanding EU-approved IV-to-SC conversion options is expected to improve the quality of life for cancer patients receiving mAb therapy and is a key driver behind initiatives such as the EU Oncodrug project. The oncobiologics sector continues to grow rapidly, with efforts targeting mAb dispensing technologies, hollow fiber reduction, and companion diagnostic systems. High-throughput antibody analysis and GMP optimization are increasingly explored to improve production and therapeutic efficacy [5, 45-47].

Emerging technologies and innovations

LAI biologics have also had a substantial impact in psychiatry. Compared to oral medications, long-acting intramuscular injections improve adherence by maintaining steady drug concentrations in the bloodstream, eliminating the need for frequent dosing. In North America, LAIs already represent a significant portion of the psychiatric market [48]. Most current formulations rely on biodegradable polymer matrices, which gradually release biologic molecules over time [49, 50]. However, administering these formulations can be challenging due to the size of injection ports, procedural pain, and the invasive nature of implantation. To address these limitations, alternative strategies are under investigation, including liquid-controlled-release formulations, microparticles, in situ forming depots, drug-loaded carriers such as liposomes and nanoparticles, and PEGylation. These advances promise to expand the role of LAI biologics in psychiatric care, offering benefits for clinicians, researchers, and biomedical engineers alike [47, 51].

Conclusion

Long-acting injectable (LAI) formulations have traditionally been used for psychiatric medications and hormone therapies. More recently, their application has expanded to include therapeutically effective monoclonal antibody drugs. This has fueled growing interest in long-acting injectable biologics, which have the potential to transform the field of immunopharmacology. LAI biologics could fundamentally change the management of chronic inflammatory, autoimmune, and oncological diseases. Given the protein-based nature of biologics, the use of automatic injection devices, such as pens or syringes, is important to ensure safe and convenient administration. However, while these devices improve ease of use for many patients, they do not fully guarantee adherence. Frequent subcutaneous injections—ranging from weekly to biweekly, or even daily—can be burdensome, leading some patients to skip doses. Clinic-based injectable therapies can also pose challenges due to privacy concerns and the inconvenience of regular visits. In contrast, long-acting injectable biologics offer the potential to enhance adherence significantly while improving delivery to inflamed tissues through both passive and active targeting mechanisms.

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