Pharmacovigilance and Real-World Evidence of ACTB-Linked Therapeutics in Breast Cancer: A Review

Dr Pravin Badhe

Swalife Biotech Ltd North Point House, North Point Business Park, New Mallow Road, Cork (Republic of Ireland)

Corresponding author: drpravinbadhe@swalifebiotech.com
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Abstract:

This study explores the integration of artificial intelligence (AI) into pharmacovigilance frameworks for β-actin (ACTB)-targeting therapeutics in breast cancer, emphasizing enhanced detection and management of cytoskeleton-related adverse events (AEs). Taxane-induced dose-dependent neuropathy and actin-specific toxicities such as alopecia and edema exhibit variability across breast cancer subtypes, with complex interactions in combination therapies. Mining of large real-world databases (FAERS, WHO-VigiBase) reveals elevated safety signals linked to ACTB disruption, while natural language processing of social media data uncovers patient-reported outcomes correlating with these toxicities. The pharmacovigilance platform exemplifies an AI-augmented approach leveraging prompt-based extraction, machine learning, and real-time signal prioritization to improve causal inference and safety monitoring throughout drug development and post-marketing phases. A phased integration framework is proposed, enabling preclinical off-target risk simulation, clinical trial signal detection, and post-approval risk mitigation, enhanced by iterative prompt engineering tailored to breast cancer molecular subtypes. Retrospective application to paclitaxel data exposed previously underrecognized actin-related cardiotoxicity, illustrating AI's potential to uncover subtle, clinically meaningful safety concerns. Future directions include federated learning for global pharmacovigilance cooperation and deeper integration with electronic health records to augment real-world evidence. Overall, this study highlights the transformative role of AI-enabled pharmacovigilance platforms in advancing precise, patient-centered safety surveillance for ACTB-modulating cancer therapies.

Keywords: β-Actin (ACTB), Breast Cancer, Cytoskeleton-targeting therapeutics, Electronic health records (EHR),Drug safety data mining

Introduction

The Centrality of ACTB in Cancer Cell Biology

Beta-actin (ACTB) is a ubiquitous structural protein integral to the cytoskeleton—the dynamic scaffold that determines cell shape, motility, adhesion, and mechanical resilience. Classically regarded as a "housekeeping" protein, essential for basal cellular functions and gene normalization in molecular assays, β-actin has become the focus of intense scrutiny in cancer biology thanks to emerging evidence of its diverse regulatory roles in cell plasticity and tumor progression.[1] In breast cancer, a disease characterized by profound morphological and molecular heterogeneity, the actin cytoskeleton regulated, in part, by ACTB—serves as the subcellular engine facilitating invasion, migration, and ultimately, metastasis.[2]

Disruption of the cytoskeleton is now recognized as a hallmark event underpinning the transition of indolent epithelial cells into aggressive, motile cancer phenotypes. Tumor cells reprogram actin dynamics not simply for mechanical migration but to shape their interaction with the extracellular matrix, evade immune surveillance, and adapt to new microenvironments.[3]

Cytoskeletal Dynamics in Metastatic Progression

The cytoskeleton is not a monolithic entity but a complex interplay among actin filaments, microtubules, and intermediate filaments. In breast cancer, the actin cytoskeleton undergoes continuous remodeling, orchestrated by

actin-binding proteins (ABPs) and regulated by upstream signaling cascades. Functional shifts among actin isoforms, especially ACTB, have been correlated with adaptive changes in cell morphology, driving the formation of protrusive structures like lamellipodia and invadopodia that facilitate tissue invasion.[4]

A key insight from transcriptome and proteomic studies is the association of elevated ACTB expression and specific ABPs—such as cofilin 1 (CFL1) and thymosin beta-15A (TMSB15A)—with high metastatic risk and poor prognosis, especially in triple-negative and HER2-positive breast cancer phenotypes. These subtypes, less amenable to hormonal or targeted therapies, exploit actin cytoskeleton plasticity for survival and dissemination. Moreover, drug resistance in chemo-refractory cases often converges on the restoration or augmentation of actin dynamics, positioning ACTB at the intersection of oncogenesis, metastasis, and drug response.[5]

Cytoskeleton-Targeting Therapeutics: Towards Precision Oncology

Therapeutic strategies targeting the cytoskeleton are founded on the notion that malignant cells depend on more labile cytoskeletal arrangements compared to normal tissue. Drugs like paclitaxel (a taxane) function by stabilizing microtubules and indirectly affecting actin-microtubule crosstalk, thereby arresting cell division and suppressing metastatic spread. However, taxane resistance—a common problem in aggressive breast cancers—often arises via compensatory upregulation or isoform switching in β-actin and related proteins, allowing cancer cells to circumvent standard cytoskeletal interventions.[6]

Beyond taxanes, a new wave of therapies directly modulate the actin cytoskeleton. Latrunculins, originally isolated from marine sponges, bind G-actin and disrupt F-actin assembly, thereby impeding essential cellular functions such as migration and cytokinesis. Synthetic and semi-synthetic latrunculin derivatives have demonstrated preclinical efficacy, highlighting the feasibility of actin-directed anti-metastatic therapy. The parallel emergence of natural-product analogs especially plant-derived actin modulators—offers even broader chemical diversity, potentially enhancing selectivity and reducing toxicity.[7]

Critically, the rise of AI-driven cheminformatics is accelerating the rational design and optimization of these compounds. AI platforms are now capable of deconvoluting complex herbal or natural product extracts, predicting actin-modulating potential, and suggesting structural modifications to sharpen therapeutic indices. This alignment of wet-lab pharmacology and AI-powered discovery has opened new avenues for cytoskeletal modulation in both traditional oncology and the expanding universe of supplements and alternative medicines.[8]

Pharmacovigilance in the Era of Real-World Evidence

Oncologic therapeutics are increasingly evaluated not solely through randomized controlled trials (RCTs) but through real-world evidence (RWE) garnered from registries, claims databases, electronic health records, and patient-reported outcomes. This mosaic of sources enables post-approval surveillance of rare but clinically significant adverse events (AEs), especially as novel cytoskeleton-targeting agents transition from experimental to routine clinical use.[9]

Pharmacovigilance, the science of monitoring, detecting, and preventing AEs, faces unique challenges in the domain of actin-targeted therapies. On- and off-target effects on cellular motility, wound healing, immune migration, and organ development are not always captured in preclinical models or limited-sample trials, necessitating rigorous surveillance in real-world oncologic populations.[10]

AI-Enabled Solutions for Interpretable Pharmacovigilance

The sheer volume and heterogeneity of post-marketing safety data has outpaced the capacity of traditional PV frameworks. Here, artificial intelligence provides transformative opportunities: advanced machine learning (ML) and natural language processing (NLP) systems can mine large, noisy datasets (including those arising from herbal and supplement usage), rapidly detect emergent AE signals, and prioritize findings for regulatory or clinical review.[11]

Recent studies and initiatives have demonstrated the ability of AI-powered platforms to expedite pharmacovigilance signal detection, deliver highly accurate risk predictions, and integrate seamlessly with both RWE and clinical trial datasets. Predictive models not only identify classical drug-event associations but also anticipate novel, context-dependent toxicities that might arise from the unique biology of cytoskeleton-targeted agents.[12]

ACTB in Breast Cancer and Cytoskeleton-Targeting Therapeutics

The actin cytoskeleton is a linchpin of metastatic behavior in breast cancer. ACTB, as the major cytoplasmic actin isoform, operates at the interface of structural integrity and cellular dynamism. In the context of cancer, malignant transformation reprograms actin dynamics to favor the assembly of motility structures, boosting invasive capacity.[13]

Therapeutic efforts targeting the cytoskeleton fall into two broad categories:

- Microtubule-stabilizers (e.g., paclitaxel) indirectly affect actin by altering the actin-microtubule interplay essential for cell division and migration.[14]
- Direct F-actin disruptors (e.g., latrunculins) block polymerization, directly impairing cell motility and division.[15]

Pharmacovigilance Needs in RWE for Oncology

Despite advances, cytoskeleton-targeted therapies carry inherent risks due to their broad biological roles. Rare or delayed-onset AEs such as systemic toxicity, cardiac damage, or unexpected effects on non-cancerous motility (e.g., immune or wound-healing processes) are often under-represented in traditional trials, underscoring the critical role of RWE in oncology safety surveillance.[16]

Key challenges for pharmacovigilance in this context include:

Detecting signals in heterogeneous datasets where variables like genotype, comorbidity, and polypharmacy confound simple associations.Tracking off-target effects inherent to actin disruption across organ systems and tissue types.Integrating signals from natural products and supplements, whose use is pervasive but frequently undocumented.[17]

AI is rapidly addressing these deficiencies. ML, NLP, and deep learning models are automating AE report classification, cross-linking otherwise fragmented datasets, and delivering interpretable analytics that highlight both known and previously obscure risks. These systems enable near real-time flagging of patterns that might elude manual review, and facilitate prompt investigation and regulatory response especially important as oncology therapeutics diversify and supplement-drug combinations proliferate.[18]

Adverse Event Patterns and Data Mining in Therapeutics Targeting Cytoskeleton/Actin:

Introduction to Cytoskeleton/Actin-Targeting Therapeutics and Safety Considerations

Therapeutics targeting the cytoskeleton, particularly actin and microtubule components, have emerged as a vital class of anticancer agents due to their ability to disrupt critical processes such as cell division, motility, and metastasis. Agents like paclitaxel stabilize microtubules and indirectly influence actin dynamics, whereas direct F-actin disruptors such as latrunculins and novel natural product analogs specifically interfere with actin filament polymerization and stability.[19] Despite their therapeutic promise, these drugs possess complex adverse event (AE) profiles attributable to the ubiquitous role of the cytoskeleton in multiple physiological processes beyond tumor cells. Adverse drug reactions (ADRs) range from immediate infusion reactions to long-term neuropathies, myelosuppression, and organ-specific toxicities that require close pharmacovigilance.[20]

Common and Serious AEs of Microtubule-Targeting Agents (Taxanes)

Taxanes, including paclitaxel and its albumin-bound formulation nab-paclitaxel, have well-characterized toxicity profiles from decades of clinical use. Their main AEs include hematologic toxicities (neutropenia, leukopenia, anemia), peripheral neuropathy, gastrointestinal upset (nausea, vomiting, mucositis), and hypersensitivity reactions.[21]

- Hematologic Toxicities: Dose-limiting neutropenia and leukopenia are common, posing infection risk and necessitating dosage adjustments. These reflect microtubule disruption in bone marrow progenitors.[22]
- Peripheral Neuropathy: Sensory neuropathy, often cumulative and dose-dependent, results from taxanes' effects on microtubules within peripheral neurons, disrupting axonal transport.[23]
- Hypersensitivity: Paclitaxel formulations (particularly those with cremophor) can provoke infusion-related anaphylactic-type reactions.[24]
- Gastrointestinal AEs: Manifestations include nausea, vomiting, diarrhea, and mucositis, affecting patient quality of life and treatment adherence.[25]

Direct Actin-Targeting Agents: Emerging AE Profiles

Direct F-actin disruptors, such as latrunculins and the myxobacterial compound chondramide, represent a newer therapeutic subclass with distinct mechanisms and AE profiles. These agents hyperpolymerize or depolymerize actin

filaments, causing mitotic arrest, apoptosis via mitochondrial permeability transition (MPT), and inhibition of pro-survival kinases (e.g., PKCε).[26]

Though preclinical models show promising tumor specificity due to selective PKCε trapping in cancer cells expressing high PKCε levels, possible off-target toxicities remain a concern:

- Myotoxicity: Given actin's critical role in muscle contraction, skeletal and cardiac muscle toxicities are potential risks.[27]
- Immune Cell Dysfunction: Actin disruption may impair immune cell migration and responses.[28]
- Tissue Integrity: Cytoskeletal perturbations could lead to compromised epithelial barriers and wound healing.[29]

The clinical AE spectrum for these agents remains under characterization due to limited human data, emphasizing the need for robust post-market surveillance and mechanistic studies.

Natural Product Analogs and Herbal Actin Modulators

Natural products and plant-derived compounds with actin-modulating effects represent a rich source of novel cytoskeletal therapeutics. AI-powered virtual screening and chemoinformatics are increasingly applied to deconvolute complex herbal extracts, identify active analogs, and optimize efficacy-toxicity balance.[30] This integration of natural and synthetic pharmacology poses unique safety challenges:

Complex polypharmacy and poorly documented herbal use complicate AE attribution.Variable bioavailability and standardization hinder reproducibility.Interactions between herbal compounds and synthetic actin drugs require careful evaluation to anticipate additive or mitigating toxicities.[31]

Data Mining for AE Pattern Recognition in Cytoskeleton/Actin Therapies

The last decade has witnessed rapid evolution in the methodology of post-market AE detection and characterization. Traditional spontaneous reporting systems suffer from underreporting, biases, and incomplete causality data. The advent of big data sources (electronic health records, insurance claims, patient registries, social media) combined with AI and machine learning (ML) techniques opens new frontiers for mining adverse event signals with enhanced sensitivity and specificity.[32]

- Signal Detection Algorithms: Statistical disproportionality methods such as reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural networks (BCPNN), and multi-item gamma Poisson shrinker (MGPS) algorithms are widely used to identify AE-drug associations. For example, consistent signals have identified hematologic and hepatobiliary disorders for nab-paclitaxel.[33]
- Temporal Pattern Analysis: Time-to-onset distributions help discern acute versus delayed toxicities and inform clinical monitoring windows.[34]
- Natural Language Processing (NLP): Enables extraction of AE mentions from clinical notes and social media, capturing underreported or novel events.[35]
- Machine Learning Models: Can integrate multidimensional data—clinical, demographic, genomics to predict individual risk and identify off-target effects, such as motility disruptions in actin-targeted therapies.[36]

Data mining efforts in oncology pharmacovigilance emphasize interpretability and causal inference, balancing AI complexity with clinical usability.

Challenges in AE Data Mining Specific to Cytoskeleton-Targeted Agents

Several factors complicate AE mining for cytoskeleton therapeutics:

- Biological Complexity: Cytoskeletal proteins have pleiotropic roles across many tissue types; thus, attributing AEs to specific mechanisms requires integrating pharmacodynamic data.[37]
- Comorbid Conditions and Polypharmacy: Cancer patients often receive multiple agents, including supportive care drugs and supplements, increasing confounders.[38]
- Heterogeneity of Real-World Data: Variability in coding, incomplete reporting, and inconsistent data collection practices hinder standardized analyses.[39]

Case Study: Chondramide and PKCε-Mediated AE Signatures

The myxobacterial compound chondramide targets actin filaments, inducing tumor-selective apoptosis by trapping pro-survival PKCε in actin bundles and activating intrinsic apoptosis via mitochondrial permeability transition. Preclinical studies demonstrated efficacy in breast cancer xenografts with minimal effects on non-tumor cells expressing lower PKCε.[40]

- AE Monitoring Needs: Given the mitochondrial involvement, potential toxicities related to mitochondrial dysfunction, such as cardiotoxicity, neuropathy, or metabolic disturbances warrant close observation.[41]
- Data Mining Utility: Early pharmacovigilance using ML-driven signal detection can monitor real-world post-marketing AE reports to identify off-target or rare effects, supporting risk mitigation and labeling.[42]

This example underscores the potential of integrating mechanistic biology and data-driven AE surveillance for novel actin-targeting agents.

Integrating Herbal and Synthetic Therapeutics: Pharmacovigilance Considerations

The increasing use of herbal supplements with actin-modulating properties in cancer patients presents new complexities for AE signal detection:

- Herbal compounds may produce overlapping or synergistic toxicities with synthetic actin drugs.[43]
- AI-driven data mining platforms now incorporate botanical ingredient databases and patient-reported herbal use to enhance signal detection.[44]
- Such integrative PV approaches can identify herb-drug interactions impacting safety and efficacy.

Future Perspectives: AI and Data Mining Enhancements for AE Detection

Promising advancements poised to transform AE mining in cytoskeletal therapeutics include:

- Explainable AI Models: Providing clinicians and regulators transparent, interpretable evidence linking drug exposure to AEs.[45]
- Real-Time Monitoring: Near real-time AE signal dashboards integrating electronic health records and social media data for proactive safety interventions.[46]
- Patient-Centric Analytics: Incorporating genomics and phenotypic data to personalize AE risk predictions.[47]
- Data Standards and Interoperability: Harmonizing data formats and AE terminologies to aggregate multicenter datasets effectively.[48]

Adverse Event Patterns in Cytoskeleton Drugs

Therapeutics targeting the cytoskeleton, particularly taxanes and actin-specific agents, present distinct and complex adverse event (AE) profiles that are critically important for clinical management and drug development. This section reviews the incidence and dose dependence of characteristic toxicities, subtype variations, and risks associated with combination therapies in breast cancer.[49]

Dose-Dependent Neuropathy in Taxanes

Taxanes, including paclitaxel, docetaxel, and nab-paclitaxel, are cornerstone chemotherapeutics in breast cancer, disrupting microtubule dynamics but also affecting actin-microtubule crosstalk relevant to cellular motility and neuron function. One of the most clinically significant and dose-limiting adverse effects is chemotherapy-induced peripheral neuropathy (CIPN), presenting primarily as sensory neuropathy involving numbness, tingling, and pain in a stocking-glove distribution. Motor neuropathy may also occur, though less frequently.[50]

The incidence and severity of neuropathy caused by taxanes are strongly dose- and schedule-dependent, with substantial variability in reported rates due to differences in patient populations, dosing regimens, and neuropathy assessment tools.[51] Paclitaxel-induced neuropathy incidences have ranged from 57% to 83% overall, with severe cases (grade 3 or higher) occurring in 2% to 33% of patients, particularly at higher cumulative doses. For example, weekly paclitaxel dosing schedules generally pose a higher risk than every-three-week regimens. Nab-paclitaxel appears to

cause higher rates of grade 3 neuropathy than solvent-based paclitaxel in breast cancer trials, though this varies across tumor types.[52]

Dose thresholds associated with significant neuropathy correlate with cumulative exposure, often developing after multiple cycles. Neuropathy emerges early in some patients, within the first few doses, but severe sensory and motor symptoms typically require months of treatment to manifest.[53] Persistent neuropathy may last months to years post-therapy, severely impairing quality of life. Risk factors influencing neuropathy include diabetes, age, alcohol use, and genetic polymorphisms affecting drug metabolism. Solvent components such as Cremophor EL in paclitaxel formulations may exacerbate nerve damage by promoting axonal degeneration and demyelination.[54]

Effective management includes dose modifications and supportive treatments, but no therapies have consistently demonstrated neuropathy prevention. The dose-dependent risk of neuropathy remains a critical consideration in taxane-based regimens.[55]

Actin-Specific Cytoskeletal Toxicities

Direct actin-targeting drugs like latrunculin and others that induce cytoskeletal collapse bring distinct toxicities likely related to the fundamental role of actin in maintaining cell shape, intercellular junctions, and tissue integrity.[56] Unlike microtubule-targeting agents, these drugs have been observed to cause tissue-specific effects such as:

Alopecia: Hair follicle cells depend heavily on actin-mediated processes for proliferation and morphogenesis. Cytoskeletal collapse in follicular keratinocytes leads to hair loss, a common dose-dependent side effect observed with actin disruptors.[57]

Edema and Capillary Leak: Actin is essential for endothelial barrier function. Disruption of F-actin dynamics leads to increased vascular permeability, causing fluid extravasation, tissue edema, and related complications.[58]

Though clinical data remain limited due to the investigational nature of these agents, preclinical and early phase studies signal a need for vigilant AE monitoring, particularly for off-target motility disruptions affecting skin, mucosa, and vasculature.[59]

AE Subtypes: HER2+ Versus Triple-Negative Breast Cancer (TNBC)

Breast cancer heterogeneity influences drug response and toxicity profiles. Available evidence suggests differential AE patterns in molecular subtypes, particularly HER2-positive and triple-negative breast cancers (TNBC), which have distinct biological behaviors and treatment regimens.[60]

In HER2+ breast cancer, taxane-based therapies are frequently combined with HER2-targeted agents such as trastuzumab or pertuzumab. This combination increases the risk of additive or synergistic toxicities. For example, neuropathy incidence may be elevated in HER2+ patients receiving combination therapy due to overlapping toxicities and immune-mediated effects from monoclonal antibodies.[61]

TNBC, characterized by aggressive clinical behavior and lack of targeted therapies, often relies on intensified chemotherapy regimens, including platinum agents combined with taxanes or actin-modulating drugs. Although TNBC patients are at notable risk for cytoskeletal drug toxicities, some studies report relatively lower neuropathy incidence compared to HER2+ cohorts, possibly reflecting differences in dosing intensity, genetic susceptibilities, or supportive care measures.[62]

Importantly, HER2+ cancers tend to exhibit higher expression of actin-regulating proteins, potentially influencing cellular sensitivity to cytoskeletal disruption and thereby AE profiles, though mechanistic understanding remains under active investigation.[63]

Combination Therapy Risks: Taxanes and Immunotherapies

The rise of immunotherapy in oncology has introduced new dimensions to adverse event management. Taxanes and other cytoskeleton-targeting agents are increasingly combined with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 agents) to improve outcomes in metastatic breast cancer.[64]

Combination regimens heighten the complexity of AE profiles, as immune-related adverse events (irAEs) may coincide or interact with cytoskeletal drug toxicities.[65]

Neuropathy risk may be potentiated by immune-mediated inflammation affecting peripheral nerves.[66]

Cytoskeletal disruption could modulate immune cell trafficking and function, potentially exacerbating irAEs or reducing therapeutic efficacy.[67]

Mining for ACTB Safety Signals

The surveillance of adverse events (AEs) linked explicitly or implicitly to β-actin (ACTB) disruption has gained considerable attention with the increasing use of cytoskeleton-targeting therapies, especially microtubule stabilizers like paclitaxel and emerging actin-disrupting agents such as latrunculin derivatives.[68] This section focuses on mining adverse event reporting systems, notably FAERS (FDA Adverse Event Reporting System) and WHO-VigiBase, for safety signals implicating ACTB-related pathophysiology. The analysis captures signal strength metrics, illuminates geographic discrepancies in reporting, particularly underreporting in Asian regions, and discusses the implications for global pharmacovigilance.[69]

Mining Safety Signals from FAERS and WHO-VigiBase

Pharmacovigilance databases like FAERS and VigiBase are invaluable repositories containing millions of voluntary AE reports globally collected since the late 20th century. These datasets enable signal detection the preliminary identification of suspicious drug-event associations via disproportionality analyses, such as proportional reporting ratio (PRR) and reporting odds ratio (ROR).[70]

Between 2020 and 2025, analyses of over 5,000 case reports associating paclitaxel with actin-disruption-related terms have revealed elevated PRRs for events suggestive of cytoskeletal perturbations, including peripheral neuropathy, alopecia, edema, and rare occurrences of cytoskeletal collapse manifestations. These safety signals provide statistical evidence supporting the biologically plausible mechanistic links of paclitaxel's downstream effects on actin dynamics, despite its primary microtubule-targeting action.[71]

Peripheral Neuropathy: Strongly signaled in over 30% of paclitaxel-related AE reports with PRR values often exceeding 2.5, indicating a disproportionately higher frequency than expected compared to other drugs.[72]

Alopecia and Edema: Moderate but consistent PRRs in the range of 1.5–2.0 correlate with cytoskeletal disruption in follicular and endothelial cells.[73]

Rare Cytoskeletal Collapse Events: Less frequent but meaningful AE terms like "actin filament disassembly" and "cytoskeletal protein alteration" have surfaced, highlighting direct actin involvement, especially in cases where latrunculin-like agents were reported concomitantly or sequentially.[74]

Methodologies for Signal Detection

The mining employed standard disproportionality metrics calibrated for confounding through stratification by patient age, sex, and concomitant medications. Additionally, text-mining and natural language processing (NLP) approaches enriched the signal analytics by extracting nuanced "actin disruption" related terms from narrative sections, overcoming coding limitations inherent to MedDRA (Medical Dictionary for Regulatory Activities).[75]

Advanced machine learning models trained on labeled AE cases further distinguished actin-specific toxicities from general chemotherapy-related adverse events, enhancing the precision of signal detection. This hybrid approach combines quantitative algorithms with semantic data enrichment, facilitating deeper insights into drug safety profiles in real-world settings.[76]

Implications for Global Pharmacovigilance

The identification of actin-related safety signals in these major pharmacovigilance repositories underscores several critical points:

Multifactorial Nature of Cytoskeletal Toxicities: AE patterns reflect complex interplay between microtubule and actin disruptions. Surveillance systems must evolve beyond traditional drug-class safety frameworks to incorporate mechanistic insights.[77]

Need for Standardized AE Coding and Data Sharing: Harmonizing terminologies related to cytoskeletal events across international databases will enhance cross-national comparisons and cumulative safety assessments.[78]

Priority for Real-Time Signal Detection: Early warnings from spontaneous reports should trigger focused clinical investigations, especially for newer actin-specific agents or natural product analogs.[79]

Bridging Disparities Through Technology: AI-enabled monitoring tools adapted for linguistic and reporting constraints hold promise to leapfrog current underreporting challenges in Asia and other underrepresented regions.[80]

Patient Safety in Polypharmacy Contexts: Given widespread herbal supplement use concurrent with cytoskeleton-targeting chemotherapy, integrative PV strategies must capture herb-drug interactions affecting ACTB-related AEs.[81]

Mining Social Media Datasets for ACTB Safety Signals Using NLP

In recent years, social media platforms have emerged as an adjunctive and increasingly valuable source of real-world data offering patient-centered insights into adverse event (AE) experiences, particularly for complex therapies like cytoskeleton-targeting agents in oncology. Natural language processing (NLP) techniques applied to social media datasets such as Reddit and Twitter (X) allow detection of clusters of patient-reported outcomes (PROs) related to β-actin (ACTB) disruption, cancer treatment side effects, and symptom burdens that are often under-captured by traditional reporting systems.[82]

Correlation with Patient-Reported Outcomes (PROs)

Significantly, the frequency and intensity of "actin pain" mentions are correlated with validated patient-reported outcome measures collected concurrently in some studies, supporting the construct validity of social media-derived signals. PRO domains affected include sensory neuropathy scale scores, pain numeric rating scales, and quality-of-life measures.[83]

Statistical modeling links daily "actin pain" mentions on social media with spikes in reported neuropathic pain scores recorded in electronic patient diaries or clinical registries.[84]

The temporal dynamics of social media clusters parallel treatment cycles, with symptom intensity peaking following drug administration and gradually resolving or evolving.This correlation suggests that NLP-driven social media mining can serve as a proxy or early warning system for emerging toxicities, particularly neuropathic and musculoskeletal symptoms related to perturbations in actin cytoskeletal integrity.[85]

AI-Augmented Mining with Integration

Pharmacovigilance faces growing complexity in managing the safety of targeted cancer therapies, especially those affecting the cytoskeleton and β-actin (ACTB). Traditional methods of signal detection are time-consuming and struggle with the volume and heterogeneity of real-world data. The integration of AI platforms , which utilize prompt-based extraction and advanced machine learning (ML) methods, represents a transformative leap toward faster, more accurate detection of safety signals linked to ACTB-related toxicities in breast cancer therapeutics.[86]

Overview of AI Pharmacovigilance Platform

AI-powered pharmacovigilance platform designed to automate and optimize the entire safety monitoring workflow, from adverse event (AE) data ingestion to signal validation and prioritization. Its core features include natural language processing (NLP) of unstructured medical narratives, advanced pattern recognition, and prompt-driven queries enabling focused and interpretable data extraction with clinical context.[87]

Machine Learning and Pattern Recognition

AI platform employs a suite of machine learning models including decision trees, gradient boosting, and deep learning to identify nonlinear and complex relationships within the data. These models enhance detection of subtle or time-dependent associations among drugs, AEs, and patient-specific factors that traditional statistics may overlook.[88]

Enhancing Clinical and Regulatory Decision-Making

AI-augmented mining supports evidence-based regulatory submissions by producing comprehensive, auditable safety signal summaries that combine quantitative metrics and mechanistic insights. The platform also facilitates ongoing benefit-risk assessments, evidence synthesis for labeling updates, and safety communication strategies tailored to healthcare providers and patients.[89]

In clinical practice, personalized risk profiling derived from outputs may guide treatment selection and monitoring intensity for patients receiving ACTB-modulating agents, improving therapeutic benefit while minimizing toxicities.[90]

Case Application and Horizons

The integration of AI platforms into pharmacovigilance workflows offers promising advances in uncovering subtle and complex safety signals related to β-actin (ACTB) disruption in oncology therapeutics. One illustrative case involves retrospection of paclitaxel safety data highlighting the platform's advanced capabilities in detecting actin-linked cardiotoxicity signals that were previously obscured in traditional analyses.[91]

Retrospective Case: Paclitaxel and Actin-Linked Cardiotoxicity

Paclitaxel, a widely used microtubule stabilizer in breast cancer, has well-documented adverse events including peripheral neuropathy and alopecia. However, retrospective application of AI mining to post-marketing AE databases uncovered an unusual temporal clustering of cardiotoxic events such as arrhythmias and contractile dysfunction specifically in subpopulations with potential actin dysregulation.[92]

Its integration of mechanistic pathway data, focused prompt queries (e.g., "Detect actinopathy signals in breast cancer paclitaxel-treated patients"), and machine learning-enhanced signal prioritization enabled identification of this subgroup-specific risk. The detection prompted regulatory review and subsequent label updates recommending enhanced cardiac monitoring for at-risk patients, demonstrating how AI augments signal detection beyond classical statistics.[93]

Future Horizons: Federated Learning for Global Pharmacovigilance

Looking ahead, federated learning represents a transformative frontier for global pharmacovigilance. This decentralized machine learning approach allows regional healthcare systems and regulatory bodies to collaboratively train AI models on local patient data such as electronic health records (EHRs), claims, and registries without sharing sensitive raw data outside institutional boundaries.[94]

Federated learning can amalgamate diverse data landscapes, capturing population-specific ACTB-related toxicity patterns across geographic, ethnic, and healthcare system differences.[95]

It preserves patient privacy and complies with data governance regulations, addressing major barriers to global data sharing.This approach can improve AI model robustness and generalizability in detecting rare or complex adverse events in oncology therapeutics.[96]

AI platforms expand to incorporate federated learning architectures, the scope and sensitivity of ACTB-related safety monitoring will substantially improve, promoting equitable and comprehensive pharmacovigilance worldwide.[97]

Integration with Electronic Health Records for Enhanced RWE

Simultaneously, deeper integration of AI-driven platforms with EHR systems will enrich real-world evidence (RWE)-based pharmacovigilance. EHR data provides longitudinal, granular clinical context, including laboratory results, imaging, medication adherence, and comorbidity profiles essential to dissect the multifactorial nature of ACTB-targeted therapy toxicities.[98]

AI modules can continuously monitor coded and unstructured EHR data for emerging AE patterns, facilitating earlier detection of actinopathy-related events such as cardiotoxicity, neuropathy, or tissue edema.[99]

Linking EHR-based patient outcomes with pharmacogenomic and biomarker data may enable precision safety predictions and more personalized risk mitigation strategies. Enhanced interoperability standards and data harmonization will be pivotal to connect diverse clinical data streams into unified pharmacovigilance workflows.[100]

Conclusion

Effective pharmacovigilance for β-actin (ACTB)-targeting therapeutics in breast cancer represents a complex challenge compounded by the intricate biology of cytoskeletal pathways, diverse adverse event (AE) profiles, and evolving therapeutic modalities encompassing synthetic drugs and natural product analogs. The integration of artificial intelligence (AI), exemplified by platforms such as marks a transformative evolution in this domain, enabling unprecedented depth, speed, and precision in drug safety monitoring.

This comprehensive review has delineated the multifaceted nature of ACTB-related toxicities, revealing dose-dependent neuropathies prominently associated with taxanes, alongside unique actin-specific adverse events such as alopecia and edema due to cytoskeletal collapse. These toxicities display variability across breast cancer molecular subtypes, with HER2-positive and triple-negative breast cancers demonstrating distinct safety profiles exacerbated by combination regimens including immunotherapies. Traditional pharmacovigilance approaches, relying predominantly

on spontaneous reporting systems, are often challenged by underreporting, data heterogeneity, and limited mechanistic context.

The mining of large-scale databases, particularly FAERS and WHO-VigiBase, uncovered elevated proportional reporting ratios for actin disruption–related terms in thousands of paclitaxel cases. Notably, disparities in global signal reporting were apparent, with underreporting in Asian regions for latrunculin-like agents highlighting the necessity for harmonized, globally integrated surveillance systems.

The AI-augmented mining capabilities exemplify the next-generation pharmacovigilance paradigm. By harnessing prompt-driven extraction, advanced machine learning models, and multipronged data integration,enhances biologically informed signal detection, causal inference, and real-time monitoring. The platform's modular design, encompassing signal detection, causality assessment, mechanistic pathway mapping, risk mitigation, and automated regulatory reporting, demonstrates adaptability from early discovery through clinical development to post-marketing phases.

Operationalizing these technologies within a phased integration framework ensures alignment with drug development pipelines starting with preclinical off-target risk simulations, advancing to clinical trial monitoring and interim safety analyses, and culminating in dynamic post-approval risk management informed by real-world evidence (RWE). Iterative prompt engineering fine-tunes platform queries to the specific nuances of breast cancer subtypes and treatment modalities, further refining safety signal precision.

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