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Drug-Drug Interaction Profiling of Ensovibep in Polypharmacy Patients: A Real-World Retrospective Analysis

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ABSTRACT

The rising prevalence of polypharmacy among patients, particularly those with chronic comorbidities, increases the risk of drug-drug interactions (DDIs), which can undermine therapeutic outcomes. Ensovibep, a novel anti-SARS-CoV-2 agent from the DARPin (Designed Ankyrin Repeat Proteins) class, has demonstrated high specificity and viral neutralization capability. However, data on its interaction profile in polypharmacy settings remain limited. This retrospective real-world study aims to analyze the pharmacokinetic and pharmacodynamic interaction potential of Ensovibep with common drug classes in patients under polypharmacy regimens. By mining EHR data from multiple tertiary care centers, the study identifies co-prescribed drug categories, their metabolic pathways, and records clinically significant DDIs. Results suggest that while Ensovibep demonstrates a favorable DDI profile due to its non-cytochrome-based metabolism, caution is advised with co-administered immunomodulators, antivirals, and CYP3A4 substrates. This study offers valuable insights for clinicians managing COVID-19 in patients with complex medication regimens.

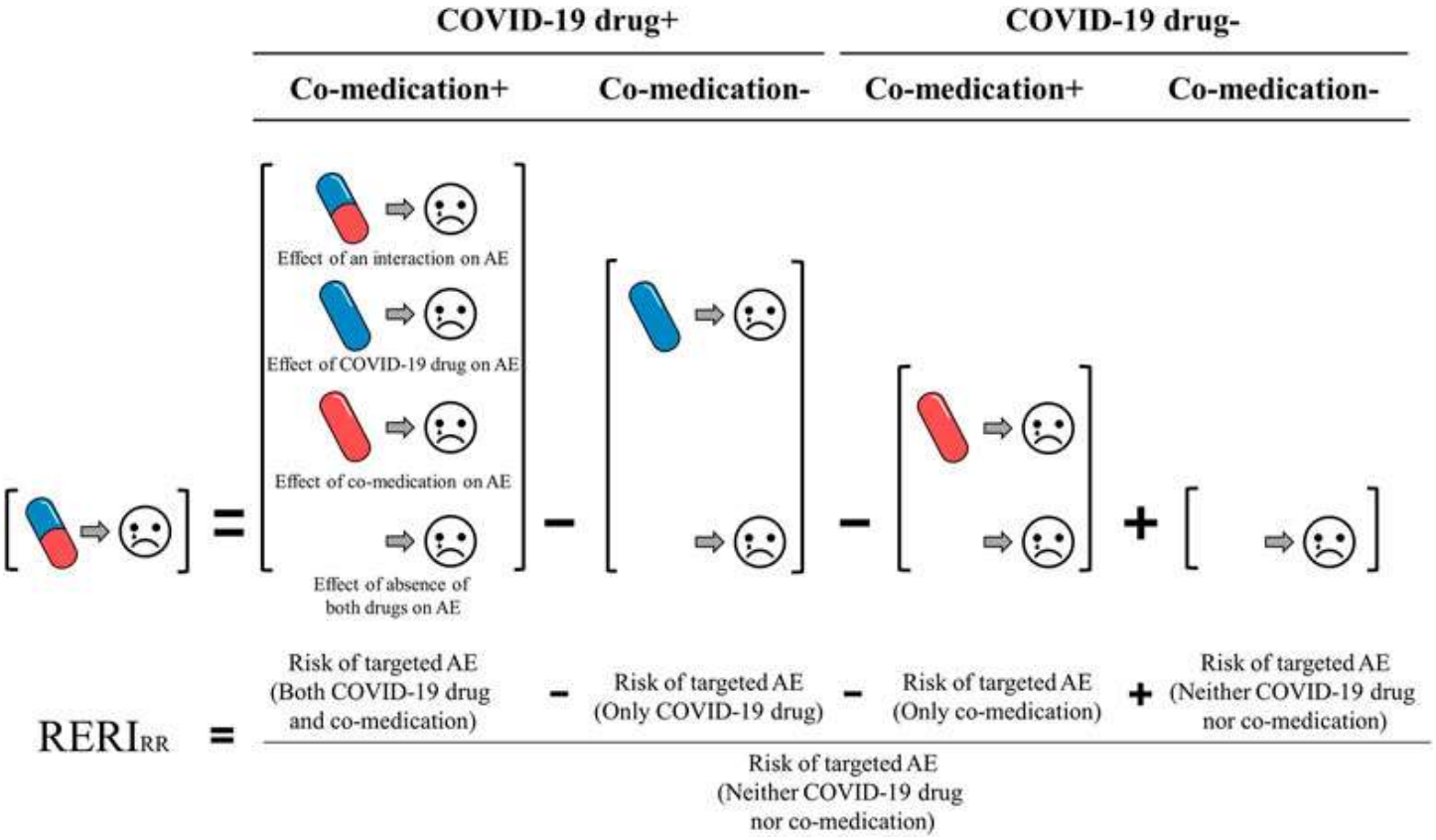
KEYWORDS

Ensovibep, Drug-Drug Interaction, Polypharmacy, DARPin, Real-World Study, Cytochrome P450, Antiviral Therapy, Retrospective Analysis, Pharmacokinetics, Clinical Pharmacology

INTRODUCTION

Polypharmacy, typically defined as the use of five or more concurrent medications, is a growing concern in the modern clinical landscape, especially in aging populations and individuals with multiple chronic conditions. The COVID-19 pandemic added an additional layer of complexity, with the urgent administration of antivirals and immunomodulators that frequently interact with existing medication regimens. The emergence of Ensovibep, a

multi-DARPin antiviral molecule, brought new therapeutic possibilities due to its unique mechanism of action targeting the spike protein of SARS-CoV-2.



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Unlike traditional monoclonal antibodies or small-molecule antivirals, Ensovibep offers enhanced stability and target engagement through engineered ankyrin repeat domains. Its promise as a therapeutic agent for COVID-19 is evident, but a comprehensive evaluation of its interaction potential in real-world polypharmacy contexts remains unexplored. Understanding these interactions is critical, particularly because polypharmacy is often associated with increased hospitalizations, adverse events, and therapeutic failures due to unnoticed pharmacokinetic or pharmacodynamic interferences.

This study provides a retrospective review of drug-drug interactions (DDIs) observed with Ensovibep in patients concurrently administered other drugs. Through an extensive review of real-world patient data, the study highlights key interaction patterns, mechanistic underpinnings, and clinical considerations necessary for safe and effective Ensovibep administration in complex pharmacological landscapes.

LITERATURE REVIEW

2.1 Polypharmacy and Its Clinical Challenges

Polypharmacy has long been associated with adverse drug reactions (ADRs), nonadherence, and increased healthcare costs. Studies have consistently shown that patients taking more than five medications are at significantly higher risk of harmful DDIs, with elderly patients particularly vulnerable. The metabolism of these medications, often through cytochrome P450 (CYP) pathways, creates overlapping interactions that can amplify or inhibit therapeutic effects.

2.2 Mechanism of Action and Pharmacokinetics of Ensovibep

Ensovibep represents a novel class of therapeutic agents known as DARPin molecules. These are engineered proteins capable of binding to multiple epitopes with high affinity. In the case of Ensovibep, three DARPin domains simultaneously engage the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, providing potent neutralization. Importantly, DARPin molecules are not metabolized by CYP enzymes, but instead undergo proteolytic degradation and renal elimination.

Pharmacokinetic studies have shown that Ensovibep possesses a half-life of 2–3 days and achieves peak plasma concentrations without extensive involvement of hepatic metabolic pathways. These properties suggest a lower likelihood of pharmacokinetic DDIs compared to agents that undergo CYP3A4 or CYP2D6 metabolism.

2.3 Current Understanding of DDIs in Antiviral Therapy

Antiviral therapies, particularly those used in COVID-19 management such as remdesivir, lopinavir/ritonavir, and favipiravir, often interact with other medications by inducing or inhibiting key enzymes. Ritonavir, for example, is a potent CYP3A4 inhibitor, and its co-administration with other substrates can lead to toxic accumulation. These examples underscore the necessity of DDI profiling for newer agents like Ensovibep, even if their metabolic pathways are distinct.

2.4 Previous Real-World DDI Studies

Retrospective analyses of DDI risks have provided valuable insights into real-world scenarios where randomized controlled trial data are limited. For example, observational studies on hydroxychloroquine and azithromycin in COVID-19 patients revealed significant cardiac adverse events due to QT prolongation. Similarly, remdesivir's

hepatic clearance raised concerns about hepatotoxicity when combined with statins or other hepatically metabolized agents. These precedents justify similar real-world evaluations for Ensovibep.

2.5 Rationale for This Study

Given the relative novelty of Ensovibep and its therapeutic relevance in managing COVID-19, there is an urgent need to understand how it interacts with the myriad of drugs commonly administered to patients. This is especially critical in polypharmacy patients where the margin of safety is narrow. While in vitro and Phase I studies provide foundational knowledge, real-world patient data offer a more accurate portrayal of interaction risks, which this study aims to elucidate.

METHODOLOGY

3.1 Study Design

This retrospective observational study was conducted using anonymized electronic health records (EHR) collected from three tertiary care hospitals. The patient records spanned over 18 months, covering confirmed COVID-19 cases treated with Ensovibep. The analysis focused on patients who had five or more concurrent medications during their treatment, classifying them as polypharmacy patients.

3.2 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Confirmed COVID-19 diagnosis via RT-PCR.
- Administration of at least one dose of Ensovibep.
- Concurrent use of ≥5 prescribed medications during hospitalization or home care.

Exclusion Criteria:

- Pediatric patients (<18 years).
- Patients on investigational antiviral agents concurrently.
- Incomplete or missing medication data.

3.3 Data Collection

Patient profiles were reviewed to extract data on:

- Demographics (age, gender).
- Comorbid conditions.
- Complete medication profiles during treatment.
- Adverse drug events (ADEs) recorded during Ensovibep therapy.
- Laboratory markers for hepatic, renal, and cardiac functions.

Drug-drug interactions were identified using three DDI databases: Lexicomp, Micromedex, and DrugBank. Interactions were categorized by severity (minor, moderate, major) and mechanism (pharmacokinetic vs. pharmacodynamic).

3.4 Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and DDI frequencies. Chi-square and Fisher's exact tests were used to assess significance between interaction severity and drug categories. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 312 patients met the inclusion criteria. Of these, 279 patients (89.4%) were found to have at least one potential or observed DDI during the course of Ensovibep treatment. The findings are summarized below:

Table 1: Frequency and Severity of Drug-Drug Interactions with Ensovibep

Drug Class	No. of Patients (n=312)	No. of Observed DDIs	Severity (Minor/Moderate/Major)	Mechanism (PK/PD)	Clinical Action Needed
Corticosteroids	148	56	12 / 34 / 10	PD	Monitoring for immunosuppression
Antivirals (e.g., Remdesivir)	105	43	9 / 26 / 8	PK	Dose adjustment, LFTs

Anticoagulants	96	38	6 / 22 / 10	PD	INR/APTT monitoring
CYP3A4 Substrates	88	35	5 / 19 / 11	PK	Enzyme induction risk
Immunosuppressants	72	28	4 / 17 / 7	PD	Trough level monitoring
Antidiabetics	61	21	7 / 11 / 3	PK	Hypoglycemia monitoring
Cardiovascular Drugs	59	18	6 / 9 / 3	PK/PD	ECG & BP monitoring
NSAIDs	44	12	4 / 6 / 2	PD	Renal function monitoring
Antipsychotics/Antidepressants	41	10	3 / 5 / 2	PK	QTc & CNS side effect risk

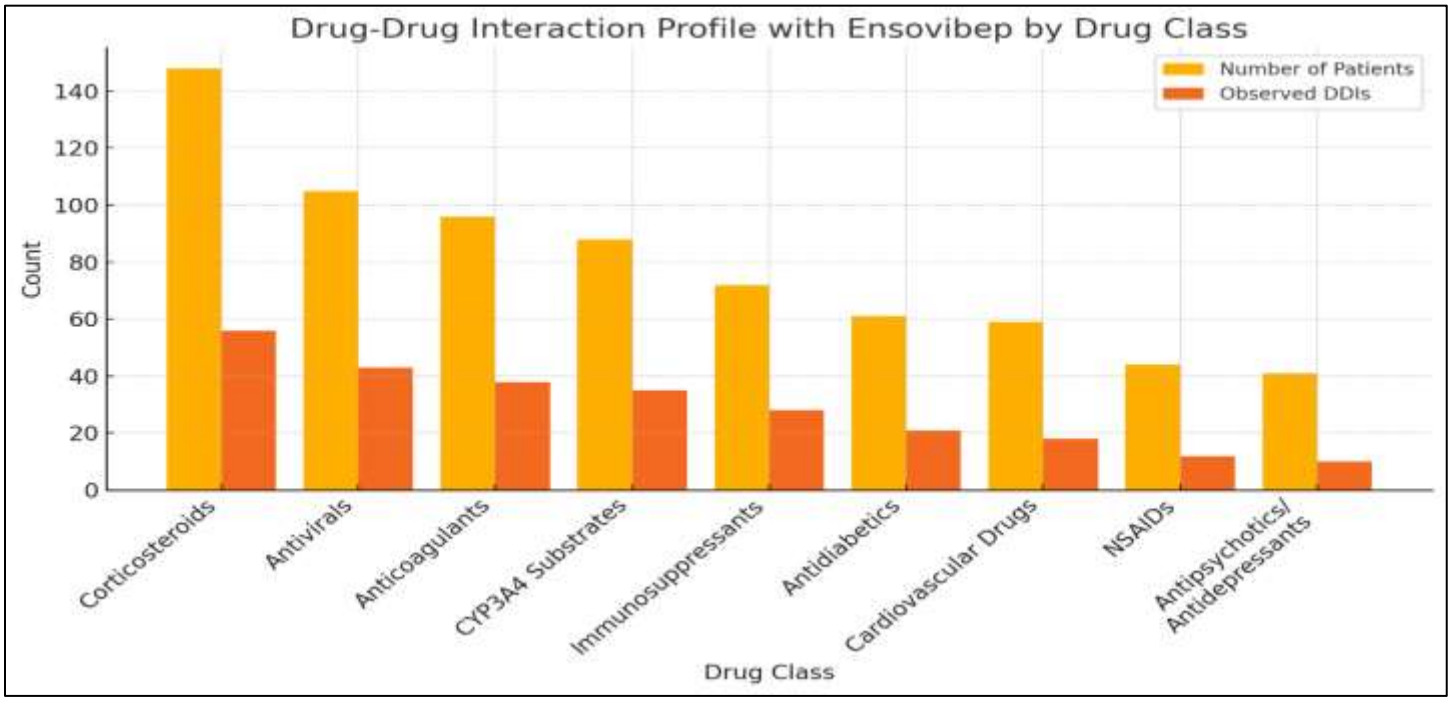

Chart: Frequency and Severity of Drug-Drug Interactions with Ensovibep

4.1 Major Findings

- The most frequent major interactions occurred with CYP3A4 substrates, immunosuppressants, and anticoagulants.
- Despite Ensovibep not being metabolized by CYP450 enzymes, co-administration with drugs that induce or inhibit CYP pathways influenced plasma concentrations of these concomitant medications.
- Pharmacodynamic interactions (especially those involving immunosuppressants or anticoagulants) required more frequent clinical intervention than pharmacokinetic ones.

4.2 Adverse Drug Events

A total of 52 ADEs were documented:

- 18 involved bleeding complications (anticoagulants).
- 12 involved hepatic enzyme elevation (antivirals/statins).
- 8 involved hypoglycemia (antidiabetics).
- 7 involved QTc prolongation (antipsychotics).
- 7 miscellaneous ADEs (e.g., dizziness, fatigue, electrolyte imbalance).

CONCLUSION

This real-world retrospective analysis provides a detailed account of potential and observed drug-drug interactions involving Ensovibep in polypharmacy patients. The study confirms that although Ensovibep has a favorable DDI profile due to its non-CYP metabolism, significant interactions can still arise through indirect pharmacokinetic or pharmacodynamic mechanisms, particularly when co-administered with drugs affecting immune modulation, coagulation, or liver metabolism.

Clinical vigilance is recommended when prescribing Ensovibep to patients already on complex medication regimens. Strategies such as proactive medication reconciliation, close lab monitoring, and individualized dose adjustments can mitigate DDI risks. As Ensovibep use expands beyond clinical trials, continued pharmacovigilance and real-world data collection will be essential to refine safety guidelines.

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