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Original Research

On-label and off-label prescribing patterns of erythropoiesis-stimulating agents in inpatient hospital settings in the US during the period of major regulatory changes

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Abstract

Background: A number of policy and labeling interventions aimed at reducing inappropriate prescribing of erythropoiesis-stimulating agents (ESAs) were implemented in the U.S. between 2006 and 2010. These interventions included the addition of an FDA Black Box Warning to ESA labeling, the implementation of a Risk Evaluation and Mitigation Strategy program, and the adoption of payment restrictions by the Centers for Medicare and Medicaid Services (CMS). The impact of these safety interventions on different types of ESA prescribing (on-label, off-label; evidence-based, not evidence-based) has not been investigated in a single study.

Objectives: The objective of this study was to explore the prescribing patterns of ESAs for on- and off-label indications in the U.S. hospital inpatients during the period of major policy and labeling changes.

Methods: A retrospective analysis of ESAs utilization patterns was conducted using Cerner Health Facts® database from January 1, 2005 to June 30, 2011. The study population consisted of adult patients admitted to hospitals during the study period who received at least one ESAs order. Indications for ESA use were assigned based on ICD-9 CM diagnosis codes, procedure codes, and medication records. ESA use was then classified based on FDA-approval and the strength of scientific evidence supporting its use. Indication categories included (1) on-label use (ONS); (2) off-label use, supported (OFS); and (3) off-label use, unsupported (OFU). Descriptive statistics were used to examine ESA use by patient, hospital, and physician characteristics and over time.

Results: ESAs were most frequently prescribed for ONS (48.7%), followed by OFU (42.7%) and OFS indications (8.6%). Of all off-label use, 83.2% were for unsupported indications. Between 2005 and 2010, the percent of inpatient visits with ESA use decreased for supported indications, both on-label (−63.2%)

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and off-label (−78.2%), but increased for unsupported indications (80%). OFU use surpassed ONS use as the most common type of ESA use in 2009.
Conclusions: Total and ONS ESA use decreased markedly, while OFU ESA use continued to increase during the period of major policy and labeling changes.
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Keywords: Prescribing patterns; On-label; Off-label; Erythropoiesis-stimulating agents; Inpatients

Take home messages

- A number of regulatory interventions and reimbursement restrictions were employed from 2006 to 2010 to communicate the risks associated with inappropriate use of erythropoiesis-stimulating agents (ESAs).
- Our study characterized the inpatient prescribing patterns of ESAs during this period of change, considering both on-label use and off-label use for indications supported and unsupported by scientific evidence of benefit.
- Total and on-label ESA use decreased from 2006 to 2010, the period of major ESA-related policy and labeling changes; however, off-label ESA use for indications unsupported by scientific evidence continued to increase during that time and surpassed on-label use as the most common type of inpatient ESA use in 2009.
- Our study highlights the importance of utilizing diverse means of communicating drug risks to the health care community. Further research is needed to gain a better understanding of the impact of specific safety interventions on both on- and off-label drug utilization.

Introduction

Erythropoiesis-stimulating agents (ESAs), including erythropoietin alfa (EA) and darbopoetin alfa (DA), are U.S. FDA-approved therapies for the treatment of anemia in patients with chronic kidney disease (CKD), chemotherapy-induced anemia, and specific subgroups of HIV infected and surgical patients.[1–3] Since the initial entry of ESAs onto the market, these drugs have found their place in the treatment of anemia outside their approved uses and are commonly prescribed for off-label use.[4,5] Despite their diverse clinical benefits, high doses of ESAs have been associated with increased risks of death and serious cardiovascular complications in patients with CKD as well as tumor progression in patients with cancer with hemoglobin levels greater than 12.0 g/dL.[6,7]

A number of regulatory interventions were employed between 2006 and 2010 to communicate the risks associated with ESA use. These interventions included an FDA-issued public health advisory alerting prescribers of the risks associated with ESAs (11/16/2006); the revision of ESAs labeling to include a black box warning (BBW) addressing safety concerns (3/9/2007); the release by the Centers for Medicare and Medicaid Services (CMS) of a new National Coverage Determination (NCD) mandating payment restrictions for ESA use in cancer patients (7/30/2007); and the FDA decision to implement a Risk Evaluation and Mitigation Strategies (REMS) program for ESA use (3/24/2010).[8–12]

Several studies have investigated the patterns of ESA use and the impact of these safety interventions on inpatient and outpatient ESAs prescribing. Specifically, the patterns of ESAs prescribing among patients with cancer,[13–15] chronic kidney disease,[16] end stage renal disease (ESRD)[17] have been described. Comparisons of ESAs prescribing patterns in outpatient and inpatient settings have found variations in indication,[18] dosing frequency,[18] and specific ESAs prescribed[18,19] by setting. Hospitalizations can significantly worsen anemia in ESRD patients, and the use of ESAs to maintain target hemoglobin ranges in the hospital has been recommended.[20] At the same time, given the risks and financial costs of the ESAs, hospital-based interventions have been developed to reduce inappropriate ESAs administration.[21,22]

Reductions in ESA use following the implementation of the CMS reimbursement policy have

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