Indian J Hematol Blood Transfus
https://doi.org/10.1007/s12288-019-01170-1

REVIEW ARTICLE

Updates on Novel Erythropoiesis-Stimulating Agents: Clinical and Molecular Approach

Zahra Moradi[1] · Amirhosein Maali[2,3] · Javad Sadeghi Shad[2,4] · Alireza Farasat[5] · Reza Kouchaki[6] · Mona Moghadami[2,3] · Mohamad Hosein Ahmadi[6] · Mehdi Azad[6]

Received: 16 April 2019 / Accepted: 5 August 2019

Abstract Erythropoietin (EPO) is an important hormone responsible for the stimulation of hematopoiesis which is impaired in a variety of diseases, such as chronic kidney disease, cancer chemotherapy, and the use of some anti-HIV drugs. Difficulties in the purification of endogenous EPO due to problems such as technical limitations, heterogeneity of target cells, inadequate amount and immunogenicity of the resultant product, had limited the entry of endogenous EPO in the clinical applications. The integration of medical biotechnology and hematology has introduced novel procedures for the production of human recombinant erythropoietin (rHuEPO), and other erythropoiesis-stimulating agents (ESAs). To investigate and produce rHuEPO, the first step is to recognize the molecular biology and functional pathways, structure, metabolism, and basic physiology of EPO. In this review, all clinical indications, side effects, challenges and notable points regarding EPO, rHuEPO, and other ESAs have also been addressed along with its molecular characterization, such as the modifications needed to optimize their rHuEPO biosynthesis.

Keywords Erythropoietin · Human recombinant erythropoietin · Erythropoiesis-stimulating agents

✉ Mehdi Azad
haematologicca@gmail.com

[1] Student Research Committee, Iran University of Medical Sciences, Tehran, Iran

[2] Student Research Committee, Babol University of Medical Sciences, Babol, Iran

[3] Department of Medical Biotechnology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran

[4] Department of Clinical Biochemistry, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran

[5] Cellular and Molecular Research Center, Qazvin University of Medical Sciences, Qazvin, Iran

[6] Faculty of Allied Medicine, Qazvin University of Medical Sciences, Qazvin, Iran

Introduction

Molecular Biology of Erythropoietin

EPO is a 30.4 kDa glycoprotein hormone with a protein portion consisting of 165 amino acids in the form of four antiparallel alpha helices, two beta sheet bonds, and two intrachain di-sulfide bridges in the Cys7–Cys161 and Cys29–Cys33 positions. The carbohydrate portion of the molecule accounts for 40% of the molecular weight; The carbohydrate structure forms the interaction of protein-carbohydrate network through the *N*- and *O*-linked glycosidic bonds. The *N*-glycoside bond is located at the asparagine 24, 38 and 83 residues. This type of bond protects EPO from the cleavage of proteolytic enzymes, and modulates the affinity of the hormone and its receptors. The *O*-glycosidic bond is located at residue position 126 (Fig. 1) [1]. The Carbohydrate component and the degree of EPO sialylation plays an important role in signaling and signal transduction to target cells. Different levels of negative sialyation result in various isoforms of glycoprotein [2, 3]. Erythropoietin hormone is sialic acid rich, and the baseline level of glycosylated EPO in serum is 5–25 IU/L that reaches 1000 times in severe anemia. The plasma half-life of EPO is 7–8 h, while non-glycosylated EPO is rapidly cleared from the circulation [4]. The total energy of the glycosylated EPO protein is 1128.54 kcal/mol, whereas the total of energy of single EPO and three units of glycans

Published online: 16 September 2019