International Journal of Hematology
https://doi.org/10.1007/s12185-022-03287-y

ORIGINAL ARTICLE

Long-term follow-up of patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab: post-marketing surveillance in Japan

Takayuki Ikezoe[1] · Hideyoshi Noji[1,9] · Yasutaka Ueda[2] · Yoshinobu Kanda[3] · Shinichiro Okamoto[4] · Kensuke Usuki[5] · Takahisa Matsuda[6] · Hirozumi Akiyama[6] · Akihiko Shimono[6] · Yuji Yonemura[7] · Tatsuya Kawaguchi[7,10] · Shigeru Chiba[8] · Yuzuru Kanakura[2,11] · Jun-ichi Nishimura[2] · Haruhiko Ninomiya[8] · Naoshi Obara[8]

Received: 28 October 2021 / Revised: 13 January 2022 / Accepted: 13 January 2022

Abstract

All Japanese patients with paroxysmal nocturnal hemoglobinuria (PNH) treated with eculizumab were enrolled in post-marketing surveillance (PMS) between June 2010 and August 2019 to assess the long-term effectiveness and safety of eculizumab. The reduction in intravascular hemolysis, the change in hemoglobin (Hb) level, and the change in renal function were assessed to determine the effectiveness of eculizumab. The types and frequencies of adverse events (AEs) were assessed to determine its safety. A total of 632 patients were enrolled and the median treatment duration was 3.6 years. Treatment with eculizumab significantly reduced lactate dehydrogenase (LDH) levels and significantly increased Hb levels. These changes were maintained for up to 5 years of treatment. An estimated glomerular filtration rate ≥ 60 ml/min/1.73 m^2 and higher LDH level at baseline were associated with increases in Hb levels during eculizumab treatment. The overall incidence of any AE was 69.92/100 patient-years. Hemolysis was the most common AE (6.43/100 patient-years). The incidence of infection-related AEs was 20.57/100 patient-years, and included meningococcal infection in three patients (0.12/100 patient-years). This long-term follow-up of patients with PNH demonstrated the sustained effectiveness of eculizumab and supports its well-established safety profile.

Keywords Paroxysmal nocturnal hemoglobinuria · Eculizumab · Effectiveness · Safety · Post-marketing surveillance

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired, progressive disorder characterized by terminal complement activation leading to chronic complement-mediated intravascular hemolysis (IVH) and thrombosis [1–4]. The disorder is caused by an acquired somatic mutation in the phosphatidylinositol glycan complementation class A (*PIG-A*) gene in hematopoietic stem cells, which results in inhibition of glycosyl phosphatidylinositol (GPI) anchor production [5]. The GPI anchor serves to attach a variety of membrane-bound proteins to the cell membrane, and lack of GPI anchor synthesis leads to the under-expression or loss of these GPI-anchored proteins on the hematopoietic stem cell membrane surface, and all subsequent cell lines generated by it [1, 5, 6]. Complement regulatory factors CD55 and CD59 are two important complement regulatory GPI-anchored proteins lost by this mechanism [6]. In the absence of factors CD55 and CD59, complement activation becomes dysregulated, and red blood cells undergo

✉ Takayuki Ikezoe
ikezoet@fmu.ac.jp

1 Department of Hematology, Fukushima Medical University, Hikarigaoka-1, Fukushima, Fukushima 960-1295, Japan
2 Osaka University Graduate School of Medicine, Suita, Japan
3 Jichi Medical University, Shimotsuke, Japan
4 Keio University School of Medicine, Tokyo, Japan
5 NTT Medical Center Tokyo, Tokyo, Japan
6 Alexion Pharma G.K., Tokyo, Japan
7 Kumamoto University Hospital, Kumamoto, Japan
8 University of Tsukuba, Tsukuba, Japan
9 Present Address: Minami Fukushima Cardiovascular Hospital, Fukushima, Japan
10 Present Address: Kumamoto Health Science University, Kumamoto, Japan
11 Present Address: Sumitomo Hospital, Osaka, Japan

Published online: 11 February 2022