Poster 115

Safety of Decade Plus Use of IgPro20 in the Real World: Post-Marketing Pharmacovigilance Report

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Introduction

- IgPro20 (Hizentra®, CSL Behring) is a subcutaneous immunoglobulin (SCIG) approved for the treatment of primary (PID) and secondary immunodeficiency (SID), and since 2018 as maintenance therapy in chronic inflammatory demyelinating polyneuropathy (CIDP)[1]
- The updated 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) CIDP guideline recommends subcutaneous immunoglobulin (SCIG) as a maintenance therapy for CIDP, highlighting that long-term dosing should be individualized and tailored to a patient's needs and response to treatment[2]
- Multiple studies have demonstrated that IgPro20 offers effective long-term protection from infections for patients with PID[3, 4], and significantly reduces infection occurrence in patients with hematological malignancies and SID[5–7]
- Pivotal phase 3 studies have shown that IgPro20 prevents relapse in patients with CIDP[8, 9]
- SCIG is associated with a reduced incidence of systemic and severe adverse drug reactions (ADRs) compared with intravenous immunoglobulin (IVIG)[10]
  - IgPro20 has a long record of proven safety and tolerability, with most ADRs reported in pivotal studies of IgPro20 in PID, SID and CIDP being mild or moderate in severity, and including injection site reactions[3–5, 8]
- Serious systemic ADRs that can occur rarely with the use of Ig products can include thromboembolic events, which generally affect less than 1% of patients[11]
  - Thromboembolic complications are more common with the use of IVIG, compared with SCIG[11]
  - Patients are more likely to be affected if they have a history of atherosclerosis, are of advanced age, have hypercoagulable disorders and/or known or suspected plasma hyperviscosity or immune thrombocytopenia, or if they have other prethromboembolic comorbidities like obesity, diabetes, and hypertension[11]

Methods

- The CSL Behring safety database was used to retrieve all post-marketing cases (since PID product launch in 2010 until 31 May 2023), which reported ADRs from the 'Opportunistic infections' (broad) and 'Embolic and thromboembolic events' Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs)
- Reporting rates of ADRs were presented as cases per 100 patient years of exposure to IgPro20, calculated by dividing the total amount of IgPro20 sold by the estimated weekly CIDP (20g) or immunodeficiency (10g) dose
- The indication for IgPro20 use was based on the reporter designation

Results

PATIENT DEMOGRAPHICS

- Of the total cumulative 35,255 patient cases with reported ADRs received by 31 May 2023, 2,494 patients reported the indication as CIDP
- Age distribution is shown in **Table 1**
- Patient exposure for IgPro20 was estimated to be 144,000 patient years based on the CIDP dose, and 287,000 patient years based on the immunodeficiency dose

FREQUENT ADVERSE DRUG REACTIONS (ADRS)

- Across both indications, the most frequently reported (>8%) ADRs included injection site reactions, headaches and fatigue (**Figure 1A**)
- In patients with CIDP, the most frequently reported (>10%) ADRs included injection site reactions, fatigue and headaches (**Figure 1B**)

THROMBOEMBOLIC EVENTS (TEES)

- TEEs were reported with an estimated overall rate of 0.36 or 0.18 per 100 patient years (estimates based on the CIDP and the immunodeficiency dose, respectively)
  - For the CIDP dose estimate, the calculation was as follows: (521 TEEs/total CIDP patient years)*100; for the immunodeficiency dose estimate, the calculation was as follows: (521 TEEs/total immunodeficiency patient years)*100
- For 36 TEE cases (6.9% of all reported TEE cases), the reported indication was CIDP (**Figure 2A**)
  - The most common TEEs were thrombosis and pulmonary embolism, reported in 22.1% and 15.2% of all TEE cases, respectively (**Figure 2B**)
  - For 9 thrombosis cases (7.8% of all reported thrombosis cases) and for 6 pulmonary embolism cases (7.6 % of all reported pulmonary embolism cases), the reported indication was CIDP (**Figure 2B**)
  - Other TEEs (≥3 cases) occurring in patients with CIDP included cerebrovascular accident, deep vein thrombosis, hemiparesis, and myocardial infarction
  - For 20 of the 36 TEE cases, a number of associated risk factors were reported, including past history of TEEs, cardiovascular conditions (arrhythmia, extrasystole, hypertension, hypercholesterolaemia, coronary artery disease, cardiac valve disease, tachycardia, carotid artery stenosis, ischaemic heart disease, coronary artery occlusion), high dose administration, recent surgery, obesity/overweight, tobacco use, significantly reduced mobility, abnormal clotting factors, catheter/stent insertion, infection, and/or malignancy

INFECTIONS

- Infections were reported with an estimated overall rate of 1.27 or 0.63 per 100 patient years (estimates based on the CIDP and the immunodeficiency dose, respectively)
  - For the CIDP dose estimate, the calculation was as follows: (1,822 infections/total CIDP patient years)*100; for the immunodeficiency dose estimate, the calculation was as follows: (1,822 infections/total immunodeficiency patient years)*100
- For 88 infection cases (4.8 % of all reported infection cases), the reported indication was CIDP (**Figure 3A**)
  - The most common infections were COVID-19, Influenza and Herpes Zoster, reported in 24.4%, 20.9% and 7.4% of all infection cases, respectively (**Figure 3B**)
  - These occurred respectively, at a rate of 0.31, 0.27 and 0.09 per 100 patient years (CIDP dose estimate) or at a rate of 0.15, 0.13 and 0.05 per 100 patient years (immunodeficiency dose estimate)
  - For 49 COVID-19 cases (11.0% of all reported COVID-19 cases), 13 Influenza cases (3.4% of all reported Influenza cases), and 6 Herpes zoster cases (4.5% of all reported Herpes zoster cases), the reported indication was CIDP (**Figure 3B**)
  - Other infections (≥3 cases) occurring in patients with CIDP included fungal infection, a SARS-CoV-2 positive test, and sepsis

Objective

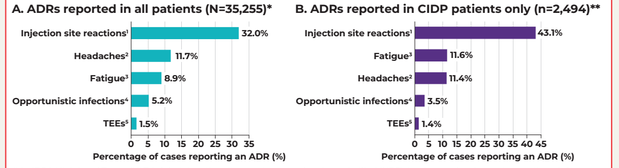
This analysis examined the safety profile of IgPro20 using real-world evidence from spontaneous post-marketing data, including reports of thromboembolic events (TEEs) and infections

Table 1. Number of patient cases by age group

Patient subgroup	All patients (N=35,255)	CIDP patients only (n=2,494)
Age group, %		
Foetus	0.01	—
Neonate	0.02	—
Infant	0.4	—
Child	8.0	0.3
Adolescent	4.2	0.9
Adult	54.7	62.9
Elderly	22.0	28.9
Unknown/Not reported	10.6	7.1

CIDP, chronic inflammatory demyelinating polyneuropathy.

Figure 1. Reporting rate of the most frequently reported ADRs, and TEEs and opportunistic infections, in all patients and in CIDP patients only

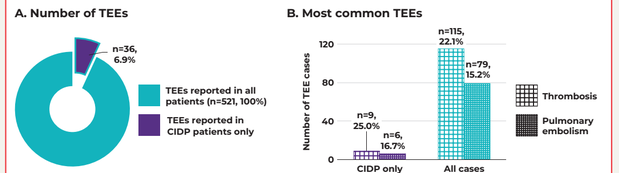


[1]MedDRA High Level Terms (HLTs): Administration site reactions not elsewhere clarified (NEC), implant and catheter site reactions, infusion site reactions, and injection site reactions; [2]MedDRA High Level Group Term (HLGT) headaches; [3]MedDRA Preferred Term (PT) Fatigue; [4]MedDRA SMQ Opportunistic infections (broad); [5]MedDRA SMQ Embolic and Thrombotic Events.

*Across all patient cases, the most frequent ADRs were defined as those reported in >8% of cases; **Across CIDP patient cases, the most frequent ADRs were defined as those reported in >10% of cases

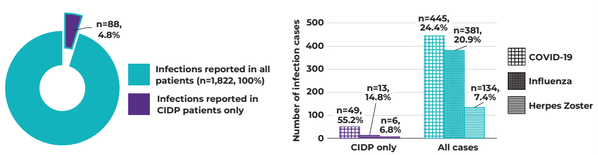
ADR, adverse drug reaction; CIDP, chronic inflammatory demyelinating polyneuropathy; MedDRA, Medical Dictionary for Regulatory Activities; TEE, thromboembolic event.

Figure 2. TEEs reported in patients receiving IgPro20



CIDP, chronic inflammatory demyelinating polyneuropathy; TEEs, thromboembolic events.

Figure 3. Infections reported in patients receiving IgPro20



CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019.

Analysis limitations

- While spontaneous reports can be useful in signal detection and characterization of an ADR, there are limitations associated with the use of post-marketing pharmacovigilance data including reliance on reporters to register an ADR, under-reporting, reporting bias, lack of exposure data for risk and rate estimates, and ascertainment bias

Conclusions

- **Spontaneous reports of ADRs, collected over a period of more than ten years, show that ADRs of interest in patients who have received IgPro20 (including TEEs and infections) were rare, including those reported in patients with CIDP**
- **The reporting rate of TEEs in patients who have received IgPro20 is comparable to the reporting rate of TEEs reported in the general population***
- **This analysis confirms the favorable benefit-risk profile of IgPro20 in patients with an underlying immunodeficiency**
- **Consistent with the established safety profile of IgPro20,[3–5, 8, 9, 15] the most frequently reported ADRs were injection site reactions, headache and fatigue**

*The incidence of venous TEEs in the general population is estimated to be between 0.09 and 0.2[12–14]

References

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