CONCOMITANT USE OF SUTIMLIMAB AND COVID-19 VACCINES IN PATIENTS WITH COLD AGGLUTININ DISEASE FROM THE PHASE 3 CARDINAL AND CADENZA STUDIES

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Introduction

- Cold agglutinin disease (CAD) is a rare subtype of autoimmune haemolytic anaemia, characterised by chronic haemolysis mediated by the classical complement pathway (CP)[1,2]
- The ongoing COVID-19 pandemic has posed an additional challenge in treating patients with CAD.[3] An association between COVID-19 and exacerbations of complement-mediated haemolytic anaemias has been described; SARS-CoV-2 seems to induce a higher and broader complement activation than other infections.[4] Furthermore, approximately 10% of patients with complement-mediated anaemias experienced a haemolytic exacerbation following COVID-19 vaccination[4]
- Anti-CD20 therapies, used off-label for the treatment of CAD, increase the risk of serious COVID-19 infections and reduce the immune response to COVID-19 vaccines[5–7]
- Sutimlimab is a first-in-class, humanised, monoclonal antibody approved for the treatment of CAD. It selectively inhibits C1s, preventing CP activation targeting the underlying mechanisms of haemolysis in CAD[8,9]
- Sutimlimab treatment led to rapid and sustained increases in haemoglobin, normalisation of mean bilirubin levels, and clinically meaningful improvements in fatigue in the pivotal Phase 3 studies, CARDINAL (NCT03347396)[10] and CADENZA (NCT03347422).[11] Sutimlimab was well tolerated, and reported adverse events (AEs) were consistent with elderly populations[10,11]
- Both studies spanned the period before and during the pandemic; and investigators were advised to vaccinate enrolled patients without stopping sutimlimab treatment
- Based on the known mechanism of action of sutimlimab, interaction with vaccinations are unlikely and antibody production in response to vaccination is not likely to be directly impacted; however, the impact of sutimlimab on immune response to COVID-19 vaccination is of interest

Objective

- To explore the safety and immunogenicity of vaccination against COVID-19 in patients receiving sutimlimab during the Phase 3 studies CARDINAL and CADENZA

Methods

- This was a post-hoc analysis from the open-label extension (OLE) Part B of CARDINAL and CADENZA studies

Use and tolerability of COVID-19 vaccines in CAD patients treated with sutimlimab: key outcome measures

- For all patients on sutimlimab included in the OLE part of CARDINAL and CADENZA:
  - The proportion of patients who received at least one dose of any COVID-19 vaccine
  - Demographics and disease activity at baseline by vaccination status
- For patients on sutimlimab included in the OLE part of CARDINAL and CADENZA who received at least one dose of any COVID-19 vaccine
  - The proportion of patients by type of vaccine (mRNA, viral vector)
  - The proportion of patients who received one, two or more than two doses
  - Mean/median interval time between first and second dose; second dose and booster
  - Mean/median interval time between vaccination administration and sutimlimab infusions
- Safety/tolerability
  - COVID-19 cases/diagnoses were collected via the regular AE reporting system. Data on tolerability to COVID-19 vaccine was collected through AE reports
  - Effect of COVID-19 vaccination on haemolysis and anaemia markers by analysis of haemoglobin, bilirubin and lactate dehydrogenase (LDH) levels

Immunogenicity to COVID-19 vaccines in patients receiving sutimlimab: key outcome measures

- The immunogenicity of COVID-19 vaccines was analysed in a subset of fully vaccinated patients (two doses), who had consented to the use of stored samples (collected no later than 6 months after vaccination); Anti-SARS-CoV-2 spike (EUROIMMUN Anti-SARS-CoV-2 ELISA) and anti-SARS-CoV-2 nucleocapsid (Abbott Architect i2000 SR) immunoglobulin G (IgG) titres were measured. Three patients who tested positive for COVID-19 during Part A of both studies were excluded from the immunogenicity analysis
- In the absence of pre-vaccination patient samples, anti-nucleocapsid antibodies were analysed to rule out a previous COVID-19 infection. COVID-19 vaccines induce an immune response specifically against spike protein (anti-spike protein antibodies), but not against the nucleocapsid of SARS-CoV-2[3,12]
- The proportion of patients with immunogenicity against SARS-CoV-2 after receiving a complete primary scheme of a COVID-19 vaccine, defined as an antibody titre above the threshold considered positive according to the manufacturer's test (anti-SARS-CoV-2 anti-spike IgG antibody titre)
  - Subanalyses of titres by prior rituximab use, region, gender, or age
- Description and comparison of anti-SARS-CoV-2 spike IgG titres before and after a booster vaccination
- Description of mean/median antibody titre in patients with immunogenicity against SARS-CoV-2
- Proportion of patients with positive anti-nucleocapsid SARS-CoV-2 IgG, as indicative of a previous, undetected COVID-19 infection

Results

Study population

- Of the 61 completers from both studies, 47 received ≥1 dose of a COVID-19 vaccine; 14 received none; 11 had an additional booster. Among those vaccinated, most (83%) received both doses during the studies; of these, mRNA vaccines were the most common (79%). Baseline characteristics are shown in **Table 1**
- The mean (SD) time from any vaccine dose to next sutimlimab dose was 7.78 (4.03) days (n=86), and from last sutimlimab dose to any vaccine dose, 8.85 (9.67) days (n=94)
- The mean inter-dose interval between first and second dose in fully vaccinated patients (n=37) was 38 days

Immunogenicity

- The immunogenicity analysis comprised 27 patients; all developed an immune response post-vaccination, with detectable IgG anti-spike antibodies (**Figure 1**)
- The mean time between last dose and serum collection was 65 days (range: 25–137)
- The immune response was consistent for patients post-vaccination regardless of history of rituximab treatment, gender, or age (<70 years and >70 years) (data not shown)
- Regional differences in mean (SD) titres were observed (p=0.043) between patients in North America [3.6 (0.4), n=6], Asia [3.4 (0.2), n=2] and Europe [2.9 (0.6), n=18] (data not shown)
- The mean time from second dose to booster was 165 days (range: 85–208; n=11). A further analysis of 6 patients with booster vaccinations demonstrated a waning immune response after the second dose, as measured before the booster, including 2 patients with undetectable levels of IgG anti-spike antibodies (**Figure 2**)

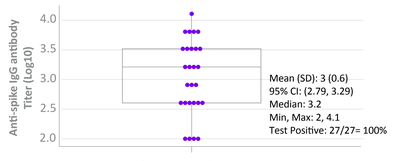

Figure 1 | Anti-spike IgG antibody titre values (Log10) in patients on sutimlimab within six months following the second dose of COVID-19 vaccination (n=27)

Table 2 | Safety and tolerability post-COVID-19 vaccination within 7 days by vaccine type for first, second and booster dose – safety analysis set

AEs in First 7 Days	mRNA			Viral	
	1st dose (n=38)	2nd dose (n=33)	booster (n=5)	1st dose (n=4)	booster (n=2)
Participants with ≥1 AE, n (%)	3 (8)	4 (12)	1 (20)	0	0
Number of AEs	4	4	2	0	0
Preferred terms, n (%)					
Back pain	0	0	1 (20)	0	0
Chills	0	1 (3)	0	0	0
Colitis	1 (3)	0	0	0	0
Fall	0	0	1 (20)	0	0
Gastroenteritis	1 (3)	0	0	0	0
Pyrexia	0	1 (3)	0	0	0
Root canal infection	0	1 (3)	0	0	0
Tooth infection	1 (3)	0	0	0	0
Vaccination site pain	1 (3)	1 (3)	0	0	0
Number of serious AEs	0	0	0	0	0

Table 1 | Baseline demographic and clinical characteristics of participants completing CARDINAL and CADENZA studies

	Unvaccinated (n=14)	Vaccinated (n=47)
Age, mean (SD)	69.8 (10.02)	68.5 (9.78)
Gender, n (%)		
Female	10 (71)	36 (77)
Male	4 (29)	11 (23)
Location, n (%)		
Europe	11 (79)	30 (64)
Japan	1 (7)	8 (17)
North America	2 (14)	6 (13)
Australia	0	3 (6)
Haemoglobin (g/dl), mean (SD)	9.0 (0.98)	9.0 (1.37)
Bilirubin (µmol/L), mean (SD)	34.4 (10.26)	42.5 (16.83)
FACIT-Fatigue sub score Scaling, n	14	46
Mean (SD)	37.3 (8.93)	31.4 (11.3)
Cold haemagglutinin (titre) at Part A baseline, n	14	43
Mean (SD)	586765.7 (1510148.7)	270036.3 (914762.4)
Prior CAD therapy in previous 5 years, n (%)		
Rituximab	8 (57)	24 (51)
Corticosteroids	9 (64)	20 (43)

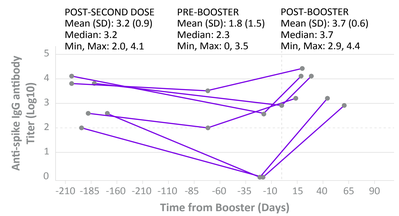

Figure 2 | Anti-SARS-CoV-2 Spike (Anti-S) IgG antibody titre values (Log10) in patients on sutimlimab post-second dose, pre- and post-booster dose of COVID-19 vaccination. Only patients with titre data after the second dose, pre-booster and post-booster are included (n=6)

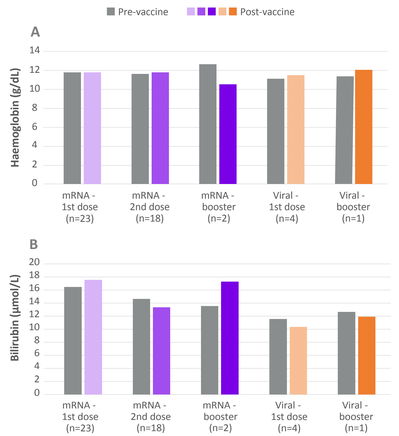

Figure 3A and B | Summary of mean haemoglobin (A) and bilirubin (B) parameters (within 14 days) of pre-vaccination, post-vaccination by vaccine type

- After receiving the booster, all 6 patients elicited antibody titres (pre- to post-booster [mean [95% CI] Log10 titre change: 1.82 [0.79, 2.85]) that were significantly greater versus post-second dose (p=0.0054; **Figure 2**)
- To rule out previous asymptomatic COVID-19 infection, anti-nucleocapsid SARS-CoV-2 IgG antibodies were assayed and were negative in all cases

Safety/tolerability

- Ten AEs were reported in 8 patients during the 7 days after any vaccine dose, but no patient experienced more than one AE, and there were no serious AEs (**Table 2**)
- No COVID-19 cases were reported during the OLE
- Only 1/47 patients missed a sutimlimab dose following the first vaccination, and 1 patient missed a sutimlimab dose following booster administration. Both times were at the investigator's discretion. No patients missed a sutimlimab dose after the second COVID vaccination dose
- Anaemia and haemolysis markers, including haemoglobin, total bilirubin, and LDH, were measured after vaccination; no indications of haemolytic exacerbation were observed (**Figure 3**)

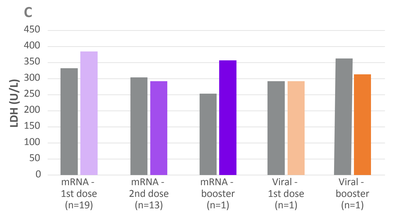

Figure 3C | Summary of mean LDH parameters (within 14 days) of pre-vaccination, post-vaccination by vaccine type.

Conclusions

- COVID-19 vaccination response was not impaired in patients receiving sutimimab for the treatment of CAD, and there was no need to modify the sutimlimab dosing schedule
- There was no significant effect of prior rituximab treatment, age or gender on titre levels, however, regional differences in mean titres were observed
- Booster vaccination response was not impaired in patients receiving sutimlimab; however, data was available for only 6 patients, therefore further investigation is warranted
- COVID-19 vaccines were well tolerated, and there were no signs of increased haemolytic marker activity following COVID-19 vaccination in patients receiving sutimlimab

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Disclosures

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