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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

The Impact of Pausing Bruton Tyrosine Kinase Inhibitor Therapy and Responsiveness of Vaccination in Blood Cancer Patients: Primary Outcome Result for the Randomised Improve Trial

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Background:
Patients with CLL have profound immunosuppression, higher mortality rates from COVID-19 infection and poorer responses to vaccination. Patients taking continuous Bruton Tyrosine Kinase inhibitor (BTKi) therapy demonstrate the poorest responses to vaccination, despite booster COVID-19 doses. BTKi therapy is taken continuously and is non-selective, inhibiting B cell receptor signalling in healthy B cells, as well as CLL cells. As covalent BTKi therapies have a short half-life and BTK receptor occupancy increases on stopping drug, a temporary pause in BTKi around the time of vaccination may improve immunity.
Aim:
To assess whether a temporary three-week pause of daily BTKi treatment around COVID-19 vaccination improves the immune response in people with Chronic Lymphocytic Leukaemia (CLL) whilst maintaining disease control.
Methods: Patients with CLL in CR/stable PR taking either acalabrutinib or ibrutinib for 1 year or more were recruited to the open-label, prospective, 2-arm, parallel group, multicentre IMPROVE trial (ISRCTN 14197181) at 11 NHS UK hospital sites,

prior to their COVID-19 booster vaccination. Participants were randomised (1:1) to either pause BTKi therapy for 3 weeks, starting 6 days before vaccination, or to continue BTKi therapy as usual. Researchers doing the laboratory analyses were blinded to group assignment. The primary outcome was SARS-CoV-2 Spike receptor binding domain (RBD) antibody titres 3 weeks after receiving the COVID-19 booster vaccine dose, assessed in the intention-to treat population.

Results:

Between Oct 10, 2022 and June 30, 2023, 99 participants with CLL were randomly assigned to continue BTKi (n=49) or pause BTKi (n=50). Mean age of participants was 70.5 years and 71/99 (72%) were male. 63/99 (64%) were on first line CLL therapy, and 51 (52%) were taking Ibrutinib, with the remaining participants taking Acalabrutinib. Participants had a median of 6 previous COVID-19 vaccinations prior to their booster (IQR 4-6). 84 (85%) were given the Bivalent Pfizer booster vaccination, 6 (6%) the Moderna Bivalent, 7 (7%) Sanofi, 1 (1%) unknown and 1 (1%) did not receive a vaccination. The proportion of participants deficient in IgG (<6 g/L); IgA (<0.8g/L) and IgM (<0.6g/L) were similar in both groups at baseline.

At baseline, the geometric mean anti-spike RBD antibody titre was 71.6 U/mL (SD 101.3) in the suspend BTKi group and 132.9 U/mL (SD 82.2) in the continue BTKi group. The numbers of participants with no prior response to vaccination ($\leq$ 0.4 U/mL) were 18/50 (36%) in the pause BTKi group and 14/49 (29%) in the continue BTKi group. After 3 weeks, 5/47 (11%) in the pause group and 1/48 (2%) in the continue group, seroconverted.

The geometric mean anti-spike RBD antibody titre at 3 weeks was 150.4 U/mL (SD 100.9) in the suspend BTKi group and 151.8 U/mL (SD 109.6) in the continue BTKi group, with a geometric mean ratio (GMR) of 1.830 (95% CI 0.820 - 4.083; p = 0.140; mixed-effects model).

There were no intervention-related serious adverse events reported. 4 patients withdrew from study. 2 patients in the pause arm and no patients in the continue arm sought NHS advice during the 3 week vaccination period. 2 patients in the pause arm and 1 patient in the continue arm commenced steroids during the 3 week period.

No difference was observed in full blood count parameters between baseline and 3 weeks' in the 2 arms. LDH levels were 191.4 (SD 44.6) and 196.5 (SD 47.4) at baseline and 195.7 (SD 81.8) and 217 (SD 99.7) at 3 weeks' in continue Vs pause arm respectively. Participants self-reported no new or swollen lymph nodes at baseline in either arm, but 4 (8%) reported new or swollen lymph nodes in the pause arm compared with 0 in the continue arm. Compliance was self-reported; 48/49 in the continue group and 47/50 in suspend group confirmed compliance to allocated arm.

Interpretation:

A 3 week interruption in BTKi around the time of vaccination may improve seroconversion rates in people with CLL but does not boost antibody titre responses overall. Further analysis of secondary endpoints including neutralisation and cellular immunity is ongoing.

Disclosures Patten: *AbbVie, AstraZeneca, BeiGene, Gilead Sciences, Janssen, Novartis:* Honoraria; *Gilead Sciences, Roche:* Research Funding; *AbbVie, BeiGene, Novartis.:* Consultancy. **Moss:** *AstraZeneca:* Research Funding; *Abbvie:* Honoraria. **Eyre:** *Autolus:* Consultancy; *Janssen:* Consultancy, Honoraria, Speakers Bureau; *Loxo@Lilly:* Consultancy, Honoraria, Speakers Bureau; *Roche:* Consultancy, Honoraria, Speakers Bureau; *Incyte:* Consultancy; *Beigene:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *AbbVie:* Consultancy, Honoraria, Speakers Bureau; *KITE Gilead:* Consultancy, Honoraria, Speakers Bureau. **Martinez-Calle:** *Takeda:* Honoraria; *Abbvie:* Honoraria, Other: Conference sponsorship; *AstraZeneca:* Honoraria, Other: Conference sponsorship; *Beigene:* Honoraria. **Parry:** *Abbvie:* Honoraria, Other: advisory group; *AstraZeneca, Janssen, Beigene,Takeda:* Honoraria; *GSK:* Other: advisory board ; *Janssen:* Other: Conference fee.

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