A 3 week pause versus continued BTKi during vaccination (IMPROVE): a randomised, open-label, superiority trial

Parry HM[1,2], Cook J[3], Peckham N[3], Phillips N[4], Talbot G[4], Abhishek A[5] Duley L[6], Hodges M[1], Roberts T[1], Barber V[3], Francis A[3], Shields A[1], Hoogeboom R[7], Willett B[8], Scott S[8], Parry-Jones N[9], Eyre T[10], Hutchinson C[11], Wandroo F[12], Paneesha S[2], Murray D[13], Jenkins S[14], Moss P[1,2], Heartin E[15], Martinez-Calle N[16], Patten P[7,17]

1.Department of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK. 2. Clinical Centre for Haematology, University Hospitals Birmingham, UK. 3. Oxford Clinical Trials Research Unit, University of Oxford, Oxford, UK. 4. Department of Haematology, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK. 5. Academic Rheumatology, University of Nottingham, Nottingham, UK. 6. CLL Support Association, London, UK. 7. Faculty of Life Sciences and Medicine, King's College London, London, UK. 8. MRC-University of Glasgow Centre for Virus Research, University of Glasgow, Glasgow, UK. 9. Department of Haematology, Aneurin Bevan University Health Board, Abergavenny, UK. 10. Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Centre, Oxford, UK. 11. Department of Haematology, University Hospitals Plymouth NHS Trust, Plymouth, UK 12.Department of Haematology, Sandwell and West Birmingham Hospitals, NHS Trust, West Bromwich, UK. 13. University Hospitals Coventry and Warwickshire, Coventry, UK. 14. Department of Haematology, The Dudley Group NHS Foundation Trust, Dudley, UK. 15. Department of Haematology, Betsi Cadwaladr University Health Board, Bangor, UK. 16. Department of Haematology, Nottingham University Hospitals NHS Trust, Nottingham, U. 17. Comprehensive Cancer Centre, Faculty of Life Sciences and Medicine, King's College London, London, UK

INTRODUCTION

Chronic Lymphocytic Leukaemia (CLL) is associated with immunosuppression, and poor response to COVID-19 vaccination.

Observational studies demonstrate particularly poor responses to COVID-19 vaccination in those taking BTKi drugs, and improved responses off therapy.[1,2,3]

No previous randomised trials have assessed whether pausing BTKi therapy, rather than continuing as usual, improves response to COVID-19 vaccination in CLL.

OBJECTIVES

Primary Objective:

- To assess the effectiveness of a 3 week pause in BTKi, rather than continuing treatment as usual, on anti-spike-RBD antibody levels 3 weeks after COVID-19 vaccination.

Secondary objectives:

- To assess anti-spike-RBD antibody levels 12 weeks after vaccination
- To assess neutralisation and T cell responses at baseline and 3 weeks after vaccination
- To assess self-reported and blood markers of disease activity and quality of life at 3 and 12 weeks after vaccination

METHOD

Study design: Randomised controlled trial

Participants: Adults with well controlled CLL, and on BTKi drug for at least 12 months

Intervention: pause BTKi drug for 1 week before and 2 weeks after COVID-19 vaccination

Control: continue BTKi drug as usual before and after COVID-19 vaccination

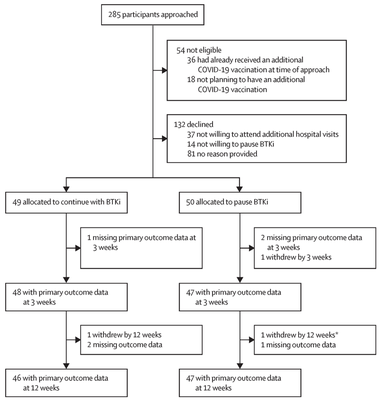
Primary outcome: SARS-CoV-2 spike RBD-specific antibody titre 3 weeks after vaccination (Roche)

Secondary outcomes: anti-spike RBD antibody at 12 weeks; neutralisation; self-reported quality of life; compliance; T cell ELISpot responses

Trial registration: ISRCTN14197181

RESULTS

Trial profile



Demographics

	Continue BTKi (n=49)	Pause BTKi (n=50)
Age	71.1 (7.8)	69.8 (9.7)
Male sex	35 (71%)	35 (71%)
Time on BTKi	920 days (665-1529)	942 (620-1836)
First-line BTKi	31 (63%)	32 (64%)
Subsequent line BTKi	18 (37%)	18 (36%)
Ibrutinib	22 (45%)	29 (58%)
Acalabrutinib	27 (55%)	21 (42%)
Median No. COVID-19 vaccines	5 (4-6)	5 (5-6)
IgG replete	25 (51%)	27 (54%)
IgA replete	25 (51%)	27(54%)
IgM replete	11(22%)	15 (30%)

Vaccine type received

	Continue with BTKi group (n=49)	Pause BTKi group (n=50)
Bivalent Pfizer vaccine	42 (86%)	43 (86%)
Bivalent Moderna vaccine	2 (4%)	4 (8%)
Sanofi vaccine	5 (10%)	2 (4%)
Unknown or did not receive booster vaccine*	0	1 (2%)

Data are n (%). BTKi=Bruton tyrosine kinase inhibitor. *One participant in the group continuing with BTKi missed week 3 and did not provide information at this timepoint.

Table 2: SARS-CoV-2 booster vaccines received

Antibody responses

	Continue with BTKi group (n=49)		Pause BTKi group (n=50)		Geometric mean ratio, mixed-effects model*	p value, mixed-effects model
	n	Geometric mean, U/mL	n	Geometric mean, U/mL		
Baseline	49	133·0 (82·2)	50	76·8 (97·1)	..	..
3 weeks	48	218·8 (122·9)	47	153·4 (103·2)	1·104 (0·565–2·158)	0·77
12 weeks	46	177·6 (95·3)	47	122·4 (92·5)	1·037 (0·529–2·035)	0·91

Data are n, mean (SD), ratio (95% CI), or p. BTKi=Bruton tyrosine kinase inhibitor. *Presenting a model adjusted for baseline values to account for the difference between groups at baseline, BTKi treatment line (first or subsequent), COVID-19 infection status at baseline, and booster type as fixed effects, and with a treatment by time interaction.

No difference was observed in response rate or antibody titre between those that paused or continued on BTKi therapy. Post-hoc analysis showed amongst those able to generate an antibody response, pausing did not enhance the magnitude of antibody titre.

Neutralisation

	Continue with BTKi group (n=49)		Pause BTKi grpup (n=50)		Geometric mean ratio, mixed-effects model*	p value, mixed-effects model
	n	Geometric mean, U/mL	n	Geometric mean, U/mL		
B.1						
Baseline	47	231 (7·3)	50	200 (6·3)	..	..
3 weeks	46	377 (8·3)	47	359 (8·4)	1·073 (0·626-1·837)	0·80
12 weeks	46	346 (8·1)	47	228 (8·0)	0·647 (0·378-1·109)	0·11
B.1.351						
Baseline	47	175 (6·1)	50	154 (5·2)	..	..
3 weeks	46	319 (8·0)	47	293 (7·6)	0·986 (0·581, 1·671)	0·96
12 weeks	46	185 (5·5)	47	140 (4·9)	0·717 (0·423, 1·216)	0·22
BA.1						
Baseline	47	90 (4·0)	50	131 (5·4)	..	..
3 weeks	46	169 (6·1)	47	194 (7·3)	0·832 (0·473, 1·463)	0·52
12 weeks	46	129 (4·7)	47	130 (6·0)	0·661 (0·376, 1·163)	0·15
BA.5						
Baseline	47	106 (4·1)	50	125 (4·5)	..	..
3 weeks	46	171 (6·2)	47	159 (5·3)	0·802 (0·510, 1·259)	0·34
12 weeks	46	124 (4·6)	47	117 (4·5)	0·700 (0·445, 1·101)	0·12

Data are n, mean (SD), ratio (95% CI), or p. BTKi=Bruton tyrosine kinase inhibitor. *Model adjusted for baseline values to account for the difference between groups at baseline, BTKi treatment line (first or subsequent), COVID-19 infection status at baseline, and booster type as fixed effects, with a treatment by time interaction.

No difference in neutralisation to SARS-CoV-2 ancestral virus (B.1) or subsequent variants of concern were observed between those that paused or continued on BTKi therapy at both 3 weeks and 12 weeks post vaccination.

Cellular responses

Outcome	Continue with BKTi (N= 49) N	Geometric mean	Suspend BKTi (N= 50) N	Geometric mean	Geometric mean ratio (LR) (95% CI)[1]	p-value (LR)
IFN-γ Wuhan						
Baseline	47	**421.9 (5.3)**	45	**255.6 (4.2)**	-	-
3 Weeks	45	**454.0 (5.6)**	46	**433.1 (4.5)**	1.336 (0.898, 1.988)	0.150
IFN-γ XBB15						
Baseline	47	**253.5 (5.7)**	59	**120.9 (4.4)**	-	-
3 Weeks	46	**322.1 (5.3)**	46	**230.7 (4.4)**	1.327 (0.851, 2.070)	0.208

Cellular responses were detected in nearly all participants.

No difference was observed in the cellular response to SARS-CoV-2 ancestral virus (B.1) or the recent XBB variant of concern between those that paused or continued on BTKi therapy at 3 weeks post vaccination.

Safety and tolerability

Self-reported lymphadenopathy was reported in 4/47 (9%) in the pause group at 3 weeks after vaccination, which reduced to one (2%) participant by 12 weeks.

No participants in the continue group reported any lymphadenopathy.

Two participants sought National Health Service care before the 3-week follow-up and both were in the pause group. No participants required hospital admission.

CONCLUSION

No difference in antibody titre was observed between the 2 study arms. No difference in sero-conversion rates were observed either. An increase in self- reported lymphadenopathy was observed in the pause arm compared to the continue arm.

Pausing BTKI around the time of vaccination is not recommended.

REFERENCES

1.**Parry H et al.** Impaired neutralisation of SARS-CoV-2 delta variant in vaccinated patients with B cell chronic lymphocytic leukaemia. J Hematol Oncol 2022;15:3. 2. **Greenberger LM et al.** Anti-spike antibody response to SARS-Cov-2 booster vaccination in patients with B cell-derived hematologic malignancies. Cancer Cell 2021;39:1297–9. 3. **Rankin K et al.** Immune response to COVID-19 vaccination in patients with Waldenström macroglobulinaemia who pause their BTKi therapy. E J Haem 2023 Jun 21;4(3):728-732.

ACKNOWLEDGEMENTS

Many thanks to the participants who took part in this study, and to all staff at the recruiting hospital. Thanks to the NIHR for funding and to the IMPROVE patient advisory group. Disclosures from HP, PP, AA, AMS, DJM, EH, SJ, NM-C, PM, RH and SP Manuscript now available at **Lancet Haematol. 2025 Apr;12(4):e294-e303. doi: 10.1016/S2352-3026(25)00008-0. PMID: 40175001.**