CORRESPONDENCE

Time to Recovery as Measured on Clinical Assessments after Sport-Related Concussion

TO THE EDITOR: As athletes with concussion recover, several tests typically guide a multistage return-to-play protocol and eventual clearance to return to sport participation.[1] The rate at which athletes return to preinjury levels of functioning across commonly evaluated domains remains unclear. We sought to describe the time to return to baseline levels of performance as measured with common clinical assessments for concussion at the group level.

We used data from the Concussion Assessment, Research, and Education (CARE) Consortium study conducted in the United States between 2014 and 2020. The methods that we used have been published previously[2] and are summarized in the Supplementary Appendix, available with the full text of this letter at NEJM.org. In brief, college-level varsity athletes who provided written informed consent completed baseline evaluations of mental status using the Standardized Assessment of Concussion, of computer-based neurocognitive functioning using the Immediate Post-Concussion Assessment and Cognitive Test, of clinical balance using the Balance Error Scoring System, of participant-reported symptoms using the Sport Concussion Assessment Tool symptom inventory, and of psychological health using the Brief Symptom Inventory–18. The medical staff at each site diagnosed injuries using a common definition[3] and administered follow-up evaluations immediately (<6 hours) after injury, 24 to 48 hours after injury, when the athlete was cleared to begin the return-to-play process, and when the athlete was cleared for unrestricted return to play. Concussion diagnoses and clearance for return to play were determined on the basis of the overall clinical impression, which was informed in part by the results of the assessments.

Recovery at the group level for each assessment was defined as the return to the mean baseline level of functioning of the group. Recovery curves were estimated with the use of semiparametric mixed models[4] that accommodated multiple within-person observations by means of person-specific random effects and allowed for estimation of smooth trajectories of changes in test scores over time. We summarized recovery trajectories for tests involving 50 or more participants with concussion, which generated a minimum of 100 observations, to ensure the stability of the estimated trajectories. For each test, the time to crossing of the group mean preinjury (baseline) score was estimated and is not intended to be interpreted at the individual participant level.

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Table 1. Time between Injury and Return to Baseline Functioning.*

Test	Overall	Male Athletes	Female Athletes
		mean no. of days (95% CI)	
Sport Concussion Assessment Tool			
No. of symptoms	6.52 (6.26–6.79)	6.59 (6.28–6.92)	6.42 (5.99–6.88)
Symptom severity	6.27 (6.02–6.54)	6.26 (5.96–6.58)	6.27 (5.85–6.72)
Brief Symptom Inventory–18			
Global	5.23 (4.82–5.73)	5.46 (4.89–6.21)	5.30 (4.65–6.06)
Depression	4.65 (4.15–5.22)	4.77 (4.21–5.45)	4.18 (3.08–5.40)
Anxiety	4.33 (3.90–4.80)	4.93 (4.32–5.68)	3.81 (3.17–4.55)
Somatization	6.73 (6.00–7.83)	7.03 (5.93–8.70)	6.69 (5.84–8.06)
Balance Error Scoring System			
Firm	3.66 (3.28–4.14)	3.45 (3.00–4.05)	4.34 (3.64–5.27)
Foam	1.96 (1.69–2.26)	2.08 (1.76–2.46)	1.76 (1.28–2.30)
Total	2.66 (2.39–2.97)	2.66 (2.34–3.05)	2.75 (2.27–3.30)
Standardized Assessment of Concussion	3.34 (2.95–3.84)	3.22 (2.79–3.83)	3.82 (3.12–4.66)
Immediate Post-Concussion Assessment and Cognitive Test			
Verbal memory	3.00 (2.65–3.39)	2.64 (2.21–3.13)	3.68 (3.07–26.67)
Visual memory†	14.02 (6.01–28+)	8.68 (5.80–26.75)	18.23 (6.02–28+)
Visual motor speed	2.63 (2.34–2.95)	2.34 (1.98–2.76)	3.14 (2.66–3.71)
Reaction time†	17.94 (0–28+)	21.44 (0–28+)	4.83 (3.91–6.30)

* The sample sizes for the assessments varied. Values represent the mean number of days from injury until a return to baseline levels of functioning (when modeled smooth curves crossed baseline values) for the full sample and for male and female collegiate athletes. Descriptions of the tests are provided in the Supplementary Appendix. CI denotes confidence interval.

† An upper boundary of the 95% confidence interval of 28+ indicates that the confidence interval extends beyond the data-collection time limit of 28 days.

Our study included 2842 varsity athletes with concussion out of a total of 33,499 who completed baseline evaluations; the participants were predominantly male (62%), White (66%), had no more than two previous concussions (92%), participated in contact sports (79%), and sustained injury during practices or training (66%) or during competition (34%). Male participants primarily participated in football (964 athletes), soccer (181), and wrestling (122); female participants primarily participated in soccer (237), volleyball (151), and basketball (147). At the group level, the return to baseline levels of functioning on most clinical assessments occurred between 2 days and 7 days after the concussion (Table 1). Visual-memory recovery and reaction-time recovery extended to 14 days and 18 days, respectively, with substantial variation. Recovery curves for all athletes and for male and female athletes are shown in Figure S1 in the Supplementary Appendix (tests of symptoms, balance, and mental status) and Figure S2 (computer-based neurocognitive testing). Recovery times according to sex and sport contact level (i.e., contact, limited contact, noncontact) are shown in Table S1.

These data suggest an overall group-level return to preinjury levels of functioning as measured with commonly used tests of symptoms, balance, and mental status, and partial

return of some neurocognitive functioning. Visual-memory and reaction-time recovery extended for longer periods of time, although heterogeneity of the scores makes clinical interpretation and application to individual athletes challenging.

Steven P. Broglio, Ph.D.
University of Michigan
Ann Arbor, MI
broglio@umich.edu

Spencer W. Liebel, Ph.D.
University of Utah School of Medicine
Salt Lake City, UT

Wenxian Zhou, Ph.D.
Chengyun Li, M.S.
Indiana University School of Medicine
Indianapolis, IN

Paul Pasquina, M.D.
Uniform Services University
Bethesda, MD

Thomas McAllister, M.D.
Indiana University
Indianapolis, IN

Michael A. McCrea, Ph.D.
Medical College of Wisconsin
Milwaukee, WI

Jaroslaw Harezlak, Ph.D.
Indiana University
Indianapolis, IN

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Zanubrutinib in Chronic Lymphocytic Leukemia

TO THE EDITOR: In the ALPINE trial involving patients with relapsed or refractory chronic lymphocytic leukemia (CLL), Brown and colleagues (Jan. 26 issue)[1] report that the Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib was superior to ibrutinib with respect to the overall response, progression-free survival, and adverse-events profile. These results mirror those of the ELEVATE-RR trial,[2] which showed a better safety profile with acalabrutinib than with ibrutinib, although the patients had a similar overall response and progression-free survival.

Between-trial comparisons of the overall response and progression-free survival are problematic because of baseline and statistical differences. The ELEVATE-RR trial included a higher-risk population than that in the ALPINE trial. The median progression-free survival for acalabrutinib was similar to that for ibrutinib in ELEVATE-RR and was significantly different in ALPINE. However, ELEVATE-RR was a noninferiority trial and did not prospectively test for superiority regarding progression-free survival. ELEVATE-RR also had a longer median follow-up and thus provided more reliable estimates of progression-free survival and overall survival. In addition, the hazard ratios for death were similar in the ELEVATE-RR and ALPINE trials (0.82 and 0.76, respectively) despite a much higher-risk patient group in the former trial.

Thus, these two trials have shown a better safety profile for second-generation BTKs over ibrutinib. However, until investigators directly compare zanubrutinib with acalabrutinib in a phase 3 trial, comparisons should be viewed more as a beauty contest in which the judge's implied bias selects the winner.