VitaGraft Liver™
Personalized Transplant Monitoring

Clinical Publication Summary

Graft-derived cell-free DNA, a noninvasive early rejection and graft damage marker in liver transplantation: A prospective, observational, multicenter cohort study

Schütz E, Fischer A, Beck J. (2017) PLoS Med 14(4):e1002286

Practical Clinical Utility

Donor-derived cell-free DNA (dd-cfDNA) is a more accurate marker for the assessment of graft health than traditional liver function tests (LFTs)

Endpoints and Goals

- To evaluate graft health using dd-cfDNA
- Directly compare dd-cfDNA with traditional LFT levels for the assessment of graft integrity (including damage and rejection)

Methods

Study and Timeframe

Prospective, blinded, multi-cohort study of 107 patients (N) with 386 samples (n) over the course of one year following liver transplantation.

Subgroup Measurement Methods and Timing

Cohort was broken into three subgroups (clinically stable, HCV+, and biopsy-proven rejection) that were analyzed by dd-cfDNA, traditional LFTs, biopsy, and ISD monitoring.

Droplet digital polymerase chain reaction (ddPCR) was used to assess dd-cfDNA concentration (%).

Repeated dd-cfDNA measurements were taken during scheduled post-operative visits and whenever rejection was clinically suspected. Visit (V), Day (D), Month (M): V1: 0–10 D; V2: 11–30 D; V3: 1–2 M; V4: 2–4 M; V5: 4–8 M; V6: 8–10 M; and V7: 10–14 M).

- Average number of dd-cfDNA measurements per patient within the first year was 4.9

Graft damage was defined as ≥10% dd-cfDNA, anything below this threshold was considered stable.

- LFTs (AST, ALT, γ-GT, and bilirubin) were measured per standard of care

Results

dd-cfDNA (%) showed statistically significant discrimination between subgroups and improvement over the LFTs analyzed (AST, ALT, γ-GT, and bilirubin) which showed much greater overlap between groups.

Elevated dd-cfDNA was seen 8-15 days prior to rejection confirmed by biopsy and before LFTs showed evidence of rejection during the same timepoint in five episodes of rejection.

VitaGraft Liver had a higher correlation with graft health and is more sensitive than traditional LFTs.

- Diagnostic sensitivity: 90.3%
- Diagnostic specificity: 92.9%
- Negative predictive value (NPV): 97%*
- Area under the receiver operating characteristic curve (AUC_{ROC}): 96.5%

*Calculated at a 25% prevalence using all biopsy-proven rejection and stable patient samples.**Graft-derived cell-free DNA (GcfDNA) is equivalent to dd-cfDNA.

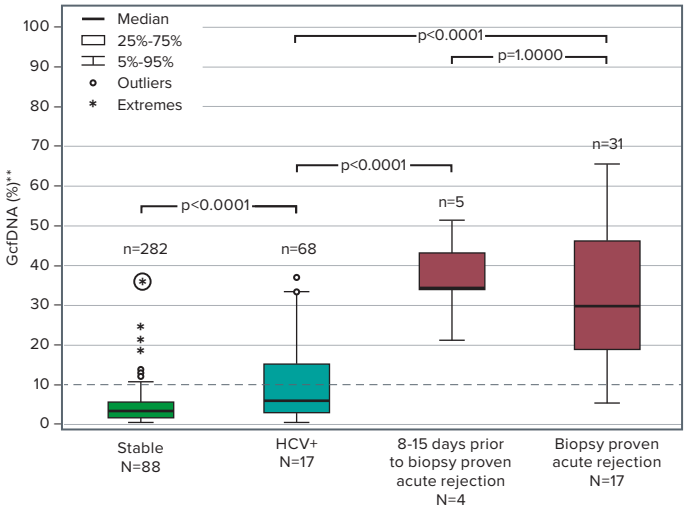

FIGURE 1. Plasma GcfDNA percentages during the first year after transplantation in stable patients and patients with either HCV or biopsy-proven acute rejection. Boxes represent median with interquartile range, with whiskers showing the 5th-95th percentile and *n*'s showing the number of contributing values. The bold circle represents the patient with subclinical rejection without biopsy 1 wk earlier (see text). GcfDNA, graft-derived cell-free DNA; HCV, hepatitis C virus.

N = number of patients | n = number of samples

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Results continued

dd-cfDNA has an independent diagnostic value separate from LFTs for discrimination between biopsy-proven rejection and clinically stable samples.

No combination of LFTs had an equal or better diagnostic value than dd-cfDNA.

Multivariable logistic regression results for liver function tests and GcfDNA

Parameter	DF	Estimate	Standard error	Wald Chi-square	*p*-Value
Intercept*	1	–6.6435	1.0510	39.9597	<0.0001
GcfDNA percentage	1	0.1800	0.0515	12.2256	0.0005
AST	1	0.0559	0.0266	4.4182	0.0356
ALT	1	–0.0073	0.0142	0.2664	0.6057
γ-GT	1	0.00145	0.0011	1.8124	0.1782
Bilirubin	1	-0.4537	0.4134	1.2044	0.2724

TABLE 1: *Constant term in linear regression analysis (value at which the fitted line crosses the y-axis). DF=degrees of freedom; GcfDNA=graft-derived cell-free DNA.

Conclusion

Determination of dd-cfDNA (%) in plasma by ddPCR allowed for earlier and more sensitive discrimination of acute rejection in liver transplant patients. Additional independent diagnostic information on graft integrity was provided by dd-cfDNA (%) in comparison to conventional LFTs.

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