Integration of genotypic data into clinical trial design and reporting in hereditary hemorrhagic telangiectasia could help personalize treatment

Hereditary hemorrhagic telangiectasia (HHT) is an inherited vascular malformation syndrome that has diverse consequences including recurrent bleeding which often results in anemia requiring iron supplementation or transfusion. Hemorrhage interventions range from nasal topical humidification, to oral agents such as tranexamic acid, local ablative treatments, and for patients still requiring intravenous iron supplementation or red cell transfusions, systemic anti-angiogenic therapies which have demonstrated promise in observational studies.[1,2] Randomized controlled trials (RCT) indicate benefit from topical saline, oral tranexamic acid, tamoxifen, and high-dose oestrogen-progesterone.[1] The number of eligible patients limits the trial size for anti-angiogenic agents. This was evident in the only bevacizumab RCT, which, with 24 transfusion-dependent recruits, was underpowered due to interpatient heterogeneity and did not meet its primary endpoint.[3] This prompted us to explore across all reported HHT treatments, whether causal DNA mutations may affect patient responses to drug treatments utilized in HHT clinical trials.

HHT results from the disruption of the BMP9/BMP10 signaling pathway, due to loss-of-function mutations usually in endoglin (*ENG*) or activin receptor-like kinase 1 (*ACVRL1*).[4] Both genes encode proteins that are constituents of the BMP9 receptor complex, although pathogenic mutations are associated with subtly different clinical phenotypes, such as variations in the distribution of arteriovenous malformations.[2,5] Furthermore, there is variability in the type of loss-of-function mutations in these genes: in *ENG*, frameshift and nonsense mutations are predominant, leading to premature termination codons (PTC), while *ACVRL1* shows a higher prevalence of missense substitutions.[6] Notably, a recent study of over 400 patients demonstrated that those with PTC-generating mutations exhibited different HHT bleeding patterns, supported by distinct endothelial cell phenotypes.[6]

Given the potential value of differentiating between causal DNA mutations in HHT treatment responses, our aim was to extract evidence from clinical trials that assess drug interventions for HHT. A comprehensive review of published clinical trials accessible through PubMed was performed using "Hereditary Haemorrhagic/Hemorrhagic Telangiectasia" as the MeSH Major Topic. We filtered search results for clinical trials and included trials investigating drug interventions. To gain further insight into the evolving landscape, ongoing clinical trials listed on *https://clinicaltrials.gov/* were also reviewed.

We identified 50 HHT trials listed on PubMed, 27 of which involved drug interventions. Eleven studies utilized local routes of administration, with medications administered systemically in 16 studies (*Online Supplementary Table S1*). HHT-causal genotypes were reported in 12 of 27 (44%) trials, predominantly in those focusing on systemic drug intervention, with no discernible trend by publication date.

Only two trials considered HHT genotypic information when analyzing treatment response.[7,8] One was a pilot study evaluating the effect of N-acetylcysteine on 43 patients, where several response metrics differed between patients with *ENG* and *ACVRL1* mutations.[7] For example, the duration of daytime epistaxis reduced by 27.9% in the 23 *ENG* cases (P=0.02) compared to 6.7% in the 18 ACVRL1 cases (P=0.7).[7] The second, smaller study assessed the anti-angiogenic drug thalidomide in 28 patients and reported significant reductions in multiple parameters of severe recurrent epistaxis. Comparing the 24 with *ACVRL1* and four with *ENG* mutations, there was no hint of a trend to different responses.[8]

Since only two published articles addressed HHT genotype-stratified responses, we explored whether more information is likely to emerge from clinical trials in progress. Out of 89 registered HHT clinical trials, we identified 41 trials that specifically focus on drug interventions. Of these, 24 have been completed (including 16 of the 27 studies already published in PubMed), eight are currently ongoing, and nine have been either withdrawn, terminated, or have an unknown status (*Online Supplementary Table S2*). Based on the information available on *clinicaltrials gov.* May 28, 2024, among the eight ongoing trials, only one study (*clinicaltrials gov. Identifier: NCT03850964*) stated a planned secondary outcome measure to examine the role of HHT genotype on the response to treatment. According to the available information, the remaining trials in progress primarily involve evaluating HHT cases as a single group, without specific mention of causal mutations.

These data show that despite widespread use of sequencing technologies in clinical diagnostics for HHT, stratifying outcomes based on the genetic subtype is not yet common practice at the design stage of HHT clinical trials. Where mutational data has been included in publications, this information was typically reported solely as baseline patient characteristics, as opposed to being considered as part of the analysis. This limitation may primarily be attributed to the small sample sizes and insufficient power of most HHT trials, making it difficult to detect differences in subgroup analysis. Other contributing factors include unknown mutational status in patients otherwise meeting study recruitment criteria, and lack of appreciation that there may be genotype-specific effects. We identified two retrospective studies that used genotypic sub-analysis within larger sample sized studies in HHT.[9,10] The

first study on bevacizumab found no difference in bleeding and anemia based on pathogenic mutations.[9] The second study, focusing on the safety of bevacizumab and thalidomide, suggested that patients with *ENG* mutations might experience more adverse effects with thalidomide compared to bevacizumab.[10]

While chance effects resulting from limited sample sizes are possible, the findings from available RCT and retrospective studies suggest that there may be an impact of HHT pathogenic mutations on some drug responses and adverse effects. The limited available data suggest that this impact may vary depending on the mechanism of action and the pathway targeted by the medication. Conducting RCT in rare diseases clearly poses challenges due to small sample sizes and significant patient heterogeneity. While analyzing by genotypic subgroups reduces case numbers and may be expected to reduce statistical power, where a confounder is removed leading to a smaller standard deviation, this increases the likelihood of detecting a difference if one exists. Therefore, in addition to strategies already utilized in HHT clinical trials, such as utilizing multi-center or multinational centers, crossover or N-of-1 designs, we suggest attention is paid to HHT genotypes. Focusing on participants with specific loss-of-function mutations[6] may further mitigate heterogeneity.

In conclusion, we suggest that integrating genotypic data into clinical trial design and reporting, holds promise for enhancing detection of treatment benefits and development of more effective therapies for HHT-associated chronic bleeding.

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https://doi.org/10.3324/haematol.2024.285809

Received: May 4, 2024.
Accepted: June 20, 2024.
Early view: June 27, 2024.

Disclosures

The authors have no conflicts to disclose. Both authors work for Imperial College London, and the institution has submitted a patent application for the use of MEK1 Inhibitors to treat HHT-related bleeding.

Contributions

AM performed literature searches and review, and wrote the first draft. CLS initiated the study, performed calculations and contributed to discussions and manuscript revisions.

Funding

This work was supported by the NIHR Imperial Biomedical Research Center, and the Alexandra Murphy HHT Foundation. The views expressed are those of the authors and not necessarily those of funders, the NHS, the NIHR, or the Department of Health and Social Care.

Data-sharing statement

All data are publicly available as referenced.

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