A proposal for a rational transfusion strategy in patients of European and North African descent with weak D type 4.0 and 4.1 phenotypes

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With the advent of red cell genotyping and the emphasis on precision medicine, transfusion strategy should be based on molecular typing whenever a serologic weak D phenotype[1] is detected in patients, including pregnant women, newborns, and potential transfusion recipients. A US-based Work Group concluded in March 2015 that such patients carrying any of the 3 molecular weak D types most prevalant in Caucasians should be treated as D positive, receiving D-positive red cell transfusions and no RhIG administration[2,3]. The recommendation has practical relevance for all European populations[2] because it concerns their prevalent weak D types, even though prevalence varies[4-6] and an even greater diversity is observed in subtypes[7]. The Work Group rated this as a strong recommendation, based on high-quality evidence from observational studies, but limited its recommendation to weak D types 1, 2, and 3, which is standard practice in many European health care systems. However, one issue had remained under discussion, as a recommendation for weak D types 4.0 and 4.1 had been postponed until more data were available. Now this time has come.

In October 2015, a Fulbright fellow began research designed to obtain data on weak D type 4.0 in the population known to harbour the greatest prevalence of this allele worldwide[8]. The study found that serologic weak D type occurs in 0.50% of Tunisian blood donations, more frequently than in Europe. Almost 90% is caused by alleles of the weak D type 4 cluster, of which 88% represents the weak D type 4.0 phenotype. The *weak D type 4.0* allele, identical to previous reports in Europeans by full length sequencing of all *RHD* exons, was unambiguously confirmed in all 53 blood donors found. Also, population statistics convincingly implied that 1 out of 3 carriers of the weak D type 4.0 phenotype is routinely typed and transfused D positive; no allo-anti-D in these patients has ever been documented in the Tunisian haemovigilance system[8]. The data are most relevant to countries bordering the Mediterranean, and in particular France, which has many immigrants from Tunisia and other North African countries.

The evidence for allo- and auto-anti-D in patients with distinct weak D types was thoroughly reviewed in 2015[2], and no new evidence for weak D types 4.0 or 4.1 has been published since. The Tunisian population has been rigorously analysed for weak D[8-14] and partial D[8,9,12,13]; only 1 anti-D in weak D type 4.0 was reported, and this patient carried an autoantibody[11]. The largest cohort of anti-D in weak D type 4.0 derived from the French haemovigilance system and documented only 1 patient whose anti-D was categorised as alloantibody[15]. The *RHCE* alleles typically linked to the *weak D type 4.0* allele on the short arm of chromosome 1 differ somewhat between Caucasian and African individuals[8,10,16]. The speculation that an *RHCE* allele might affect the immune response and control the individual's propensity to develop anti-D[11] is intellectually stimulating but requires more clinical and/or experimental evidence before any clinical decision is made based on molecularly distinct *RHCE* alleles, whether they are linked in cis to *weak D type 4.0* or positioned in trans on the corresponding chromosome.

No allo- or auto-anti-D has ever been reported in any transfusion recipient carrying the weak D type 4.1 worldwide[17], despite it being more common than weak D type 4.0[18,19] and the fact that recipients are more prone to being routinely transfused D positive. These observations are suggestive of a clinically relevant potential for anti-D immunisation in some weak D types, but not in the prevalent types 1, 2, 3, 4.0 and 4.1[18], and should be used to develop an improved transfusion strategy in patients with the serologic weak D phenotype[17,18]. Monitoring should be maintained wherever possible, and any observations of patients incurring allo-anti-D or other detrimental clinical effects should be published because such recommendations are necessarily based on the absence of contradicting evidence[8].

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Using genotyping for the fine tuning of therapeutics to fit the individual patient's needs is a hallmark of pharmacogenomics. Wider use of red cell genotyping for all serologic weak D phenotypes could eliminate most of the confusion caused by inconsistent, and sometimes erroneous, Rh typing results[20-22]. Innovation leading to even cheaper high throughput techniques will eventually allow red cell genotyping to progress beyond the current recommendations. Approved recommendations could eventually be specified in national guidelines to ensure nationwide implementation and, consequently, promote patient safety.

In line with the published conclusion[2], the lack of any additional report on adverse clinical effects, and the substantial data in the recent study[8], the undersigned propose to expand the previous recommendation: patients with serologic weak D phenotype should be tested for weak D types 4.0 and 4.1 by molecular methods; a D positive transfusion strategy can be based on the molecular result alone. We therefore recommend that patients and pregnant women with weak D types 1, 2, 3, 4.0 and 4.1 should be treated as D positive and should not be exposed to RhIG as, according to the best available evidence, these women and their babies cannot be expected to gain any clinical benefit.

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Statement of disclaimer

The views expressed do not necessarily represent the view of the National Institutes of Health, the Department of Health and Human Services, or the U.S. Federal Government.

Web resource

AABB Statements. Joint Statement on Phasing-In *RHD* Genotyping for Pregnant Women and Other Females of Childbearing Potential with a Serologic Weak D Phenotype (http://www.aabb.org/advocacy/statements/Pages/statement150722.aspx). Published online on July 22, 2015.

Disclosure of conflicts of interest

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