Fetal and neonatal alloimmune thrombocytopenia: novel ideas, novel concepts, novel therapies

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Hematology Education: the education program for the annual congress of the European Hematology Association

2015;9:257-264

A B S T R A C T

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) remains a very serious condition of pregnancy driven by the formation of alloantibodies against paternally-inherited fetal human platelet antigens (HPAs) potentially causing intracranial hemorrhage (ICH) in the fetus leading either to death or serious neurological disabilities. The last eight years has seen a shift from the use of invasive intrauterine transfusions of antigen-negative platelets to safer immunomodulatory therapies based on IV immunoglobulin in order to prevent ICHs in affected fetuses. New diagnostic laboratory assays have been developed which are gradually entering clinical practice. Large screening studies have generated data that increase the weight of evidence in favor of universal screening for FNAIT. Novel therapies involving either blockade of maternal antibodies with recombinant modified "protective" antibodies or FcRn blockade have been shown to have great potential, not only in murine models but also in proof-of-principle first-in-man studies. The concept of prophylaxis to prevent alloimmunization against HPA-1a antigens has re-emerged and is now being explored in large human trials.

Learning goals

At the conclusion of this activity, the participants should be aware of:
- the benefits of immunomodulatory therapy with IV immunoglobulin *versus* the risk of intrauterine transfusions;
- novel diagnostic tools for the detection of HPA antibodies: recombinant protein fragments and aptamers, genotyping approach to antenatal diagnosis;
- novel therapies: modified HPA-1a recombinant antibodies with an "inert" constant region and FcRn blockade;
- the concept of prophylactic treatment: data from screening studies and ongoing human studies.

Introduction

Fetal neonatal alloimmune thrombocytopenia (FNAIT), also described as neonatal alloimmune thrombocytopenia (NAITP), is a bleeding disorder of the fetus and neonate. It is the result of the formation of maternal antibodies against paternally inherited fetal platelet alloantigens. The antigenic epitopes are carried by proteins expressed on the platelet surface, and therefore antibody maturation and class-switching allows the formation of maternal IgGs which actively cross the placenta through the FcRn receptor. The alloantibodies opsonize platelets in the fetal circulation resulting in platelet destruction and thrombocytopenia. This review aims to briefly summarize the basic facts and current knowledge related to FNAIT but will particularly focus on the novel approaches that have been developed in the last few years for prenatal management of affected pregnancies, including risk stratification and tailored therapy, novel therapeutic agents and prophylaxis.

Human platelet antigens

A possible immunological basis for neonatal thrombocytopenia was first documented in the 1950s[1] but it was not until the 1980s that the genetic basis for the first platelet antigen was uncovered.[2] Since then, 28 genetic variants have been shown to underlie platelet allogenicity and the international nomenclature of human platelet antigens (HPAs) has been agreed (available at: http://www.ebi.ac.uk/ipd/hpa). Twenty-six antigens are biallelic and two are triallelic; the "a" antigen defines the common allele whilst the "b" antigen is the minor allele. It is only for HPA-1 to -5 and -15 that antibodies have been found against both alleles, whilst for the rest only antibodies against the rare allele have been implicated in FNAIT. Most polymorphisms are caused by a single point mutation with the exception of HPA-14 where a trinucleotide in frame deletion underlies the formation of the rare allele.[3] The vast majority of HPAs are carried by the αIIbβ3 integrin (also known as glycoprotein GPIIbIIIa, the platelet fibrinogen receptor) with some (HPA-5,-13,-18 and -25) on integrin α2 (part of the α2β1 collagen receptor) and two on glycoprotein Ibα (HPA-2 and -12).

By far the most common HPA involved in FNAIT is HPA-1, with antibodies against HPA-1a present in 75% of all cases of FNAIT in the Caucasian population;[4-7] the remaining cases are mostly due to antibodies against

HPA-5b, 1b, 3a or 15b.[3,8] With the exception of HPA-9[9] most other rare HPAs have only been implicated in FNAIT in the index case family. Some antigens are more commonly implicated in FNAIT in specific populations such as HPA-4[10] and -2[11] in the Asian population and HPA-6 in the Finish population.[12] Crucially, of all cases referred for investigation of FNAIT, HPA antibodies are only found in a minority (20%-40%).[5,6,8] So far two studies have looked at the value of genotyping maternal and paternal samples for the rarer HPAs in order to clarify samples for which serological investigations against the common HPA are negative. In both cases, genotyping of over 1000 cases showed very little added value in explaining the large number of FNAIT referrals.[12,13]

Natural history and epidemiology

Fetal neonatal alloimmune thrombocytopenia is the most common cause of severe neonatal thrombocytopenia in an otherwise healthy neonate.[14,15] Although prospective studies have shown that alloimmunization against the most common alloantigen in FNAIT (HPA-1a) occurs in 1350 pregnancies, severe thrombocytopenia due to platelet alloantibodies occurs in 1/1000 births.[16-19] The most severe complication (fetal intracranial hemorrhage, ICH) occurs only in 10%-20% of these cases[20-22] with the majority (80%) of ICHs occurring in utero[22-24] sometimes as early as 16 weeks gestation.[25,26] These statistics have been confirmed in a recent systematic review including data from more than 50,000 newborns showing an incidence of 0.15% for severe thrombocytopenia with a proven diagnosis of FNAIT in a quarter of them (roughly 1/2500 pregnancies) and ICH in 25% of the proven FNAIT cases, all occurring in the antenatal period.[27]

In Caucasians, the allele frequencies for HPA-1a (corresponding to a Leucine at position 33 of the β3 integrin) and HPA-1b (Proline33) are 85% and 15%, respectively, with homozygous HPA1b1b women representing 2.25% of the population. Only approximately 10% of HPA1b1 women pregnant with a HPA1a positive fetus will produce HPA-1a antibodies, but 70%-90% of these alloimmunized women will harbor the HLADRB3*0101 allele variant.[8,18] This is explained by the selective association between the HLADRB3*0101 variant of the β subunit of the HLA class II complex and the "presented" peptides carrying the HPA-1a epitope (but not -1b) demonstrated in crystal structure, leading to a strong stimulation of T-helper cells and antibody response.[28] Unlike the corresponding hemolytic disease of the newborn (HDN) resulting from maternal alloimmunization against fetal red cell antigens, retrospective studies have shown that FNAIT presents during the first pregnancy in 50% of cases referred for investigation.[6,7,23] It is thought that this relates to the fact that the β3 integrin is expressed on syncytiotrophoblast in the first trimester of pregnancy. Although the placenta represent an immunological "safe haven", there have been suggestions that alloimmunization may be the result of syncytiotrophoblast debris shed into the maternal circulation.[29,30] In contrast, prospective screening studies have, however, shown that, in fact, a large proportion (up to 75%) of women become alloimmunized around the time of birth[18,19,31] which has implications for the development of a potential prophylactic strategy (see below).

Laboratory investigations

Investigations of FNAIT rely on the detection and identification of maternal platelet alloantibodies and its epitope combined with genotype analysis.

Genetic investigations

Genotypic analysis by polymerase chain reaction (PCR) using either sequence specific primers (SSP), restriction fragment polymorphism (RFLP) or fluorophore-based probes in a real-time PCR assay are commonly used to establish the maternal and paternal genotype, usually including HPA-1 to 5 and HPA-15. One recent discovery has been the development of assays to determine the genotype of the fetus for the HPA-1 antigen from fetal DNA present in the maternal circulation without the need for fetal sampling. This now allows the clinician to ascertain whether the current pregnancy is at risk of FNAIT when the father is heterozygous for the offending antigen or when paternal testing is not possible. Scheffer *et al*. used a PCR-based method in combination with digestion with the Msp1 restriction enzyme to eliminate the 'noise' from the maternal HPA-1b1b alleles and Le Toriellec *et al*. used two methods, one based on allele-specific real-time PCR and one using high-resolution melting curve on PCR amplicons. Both groups showed that these techniques were reliable on samples obtained from week 12-15 of gestation onwards.[32,33]

It is likely that the advent (and tumbling costs!) of new generation sequencing combined with the targeting of genomic regions of interest in custom-made 'chips' will likely change clinical practice in the coming years. This will not only allow the detection of the most common HPA involved in FNAIT but also of rarer variants known or yet to be discovered.

Antibody detection

Monoclonal antibody-specific immobilization of platelet antigens (MAIPA) is still the most broadly used method for the identification of alloantibodies but it is a difficult assay that requires a specialist laboratory and necessitates panels of HPA-typed platelets and validated monoclonal capture antibodies. To bypass the need for typed platelets and potentially detect antibodies against low-frequency antigens, new assays have been developed using recombinantly expressed β3 integrin peptides.[34,35] These peptides can be bound to microspheres and have been shown to have similar sensitivity and specificity to the MAIPA assay using Luminex xMAP® technology.[36] Other technologies, such as surface plasmon resonance (SPR)[37] or specially designed aptamers, have the advantage of detecting low-affinity antibodies but SPR requires the use of purified immunoglobulins and is expensive, and to date only HPA-1a specific aptamers have been developed.[38]

Delivery and postnatal management of FNAIT

Caesarean section seems to be the recommended mode of delivery, although there is no evidence for its benefit *versus* normal vaginal delivery in cases of FNAIT,[39] despite the fact that intrapartum ICHs are actually rare. Norwegian investigators, who have so far carried out the

largest screening study in FNAIT, defended the choice of Caesarean section as a mode of delivery based on 3 arguments: 1) delivery of the child 2-4 weeks before term to limit the risk of in utero ICH; 2) an increased incidence of subdural hematoma (although these are different from the intraventricular/intraparenchymal ICH usually seen in FNAIT) on MRI scan after vaginal delivery (26% *vs*. none after Caesarean section); and 3) the ability to time delivery to ensure that antigen-negative platelets are available for the newborn.[18] The first and second points would of course also apply for vaginal delivery after induction of labor. Another reasonable alternative is to allow vaginal delivery after confirmation of a safe platelet count using fetal blood sampling.[40]

In cases where no prior diagnosis of FNAIT has been made prior to delivery, severe thrombocytopenia will present in most with either no symptoms at all or skin purpura. Accepted practice seems to be that neonates with other clinical problems (such as sepsis or necrotizing enterocolitis) should be transfused if the platelet counts falls below 50×10^9/L (with some clinicians using an even higher threshold, such as 100×10^9/L, for those with a documented ICH). On the other hand, healthy non-bleeding neonates with a platelet count below 30×10^9/L should receive a transfusion to prevent more serious bleeding complications (such as ICH which should be screened for by ultrasound scanning in any severely thrombocytopenic neonate). In practice though, transfusion thresholds vary widely between institutions, from 50×10^9/L to more restrictive targets of 25×10^9/L or even less.[41-43] These discrepancies are due to the lack of proper randomized trials assessing the effectiveness of platelet transfusion in preventing bleeding, particularly in neonates (although large multicenter studies are now under way; available at: http://www.planet-2.com/home.html), compounded by the fact that bleeding in neonates is not necessarily correlated with the platelet count.[44] In the case of FNAIT, the gold standard therapy is the administration of antigen-negative platelets and in some countries HPA-1a and -5b negative platelets are available "off the shelf".[44]Most cases of FNAIT resolve within a few days after birth and, more often than not, one transfusion will raise the platelet count sufficiently so that no further blood products are required.[46] Random platelets can also be administered in order to rapidly raise the platelet count and prevent ICH in the immediate perinatal period,[47,48] although in such cases a 1-h post-transfusion platelet count should be checked to monitor the response and repeated platelet transfusions may be required.[49] IV immunoglobulins (IVIg) can be used, but only in combination with transfusion due to the slow rate of response (24 h) and may have a role in cases where there is prolonged thrombocytopenia.[15,50]

Antenatal management of FNAIT

Invasive treatment: intrauterine transfusions of antigen-negative platelets and fetal blood sampling

Following the demonstration of the effectiveness of intrauterine transfusions (IUTs) of antigen-negative platelets,[51] IUTs became common practice for cases of FNAIT in the 1980s. Although the practice in experienced hands has been shown to be safe in cases of red cell alloimmunization with procedure-related loss of less than 2%, the outcome is very different with platelet IUTs. This is due to the danger of exsanguination after puncturing the cord of a fetus with a very low platelet count,[52] the larger plasma volume in platelet IUTs which can lead to profound bradycardia[53] and to the fact that platelet survival in circulation is much shorter than that of red cells, necessitating repeated IUTs, ideally weekly to maintain the platelet count above $50x10^9$/L for the whole of the second part of the pregnancy.[53,54] Combining the results of several series of patients, the fetal loss rate from IUTs is estimated at around 6%.[6,52,55,56] One group in Germany reported no fetal loss in 470 IUTs, all performed by a single operator.[57] With the option of using less invasive and apparently efficient immunomodulatory therapies, very few centers now use fetal blood sampling and IUTs as first-line therapy.

Immunomodulation

Bussel described the use of IVIg for prenatal treatment of FNAIT in 1988, and since then immunomodulation has gradually become the standard treatment for this condition. It is still not totally clear how IVIgs work. Putative mechanisms include increasing the clearance of HPA antibodies by blocking the maternal FcRn receptors and, through the same mechanism, reducing transport of maternal antibodies across the placenta; or decreasing the destruction of sensitized platelets in the fetus by blocking macrophage Fc receptors. The standard dose of IVIg is usually 1 g/kg administered weekly from 20 weeks gestation in combination or not with steroids.[6,58,59] Two studies have suggested a risk-based approached and dose escalation based on the only factor clearly predictive of outcome, namely severity (ICH and degree of thrombocytopenia) in the previous pregnancy.[59-61] The outcome of immunomodulation has been remarkably good with only 2 cases of ICH documented in the literature whilst having IVIg,[54,62] so much so that some authors now recommend the use of 'blind' therapy with fetal blood sampling to monitor response to treatment.[58,61,63] In contrast, a review of all published series indicated that, for at least 20% of cases, IVIG fail to raise the fetal platelet count above $50x10^9$/L (up to 90% in one series where serial sampling was carried out during treatment, t(57) suggesting that IVIg may protect against bleeding even in the presence of persisting thrombocytopenia.[64] In "non-responders", the standard strategy is to double the dose of IvIg to 2 g/kg per week with or without the addition of prednisolone 0.5 mg/kg per day. Clearly the debate is ongoing as to what dose of IVIg to use, when to start therapy (12 weeks *vs*. 16 weeks) and whether fetal blood sampling is appropriate, despite its clear link to an increased risk of fetal loss or premature Caesarean section during sampling (15%).[65]

The most common side-effects of IVIg in the mother, such as headaches, myalgia and allergic reactions, can be easily treated,[66] but the infectious risk associated with pooled blood products such as IVIg cannot be dismissed, given a previous outbreak of hepatitis C associated with plasma-derived anti-D immunoglobulin[67,68] and concern over emerging infectious agents, such as prions, for which donors are not screened and which are resistant to heat treatment.[69] In addition, IVIg is expensive, and its chronic worldwide shortage is well-documented.[70,71]

Novel approaches

In the last few years, several new directions of research have emerged aimed at addressing some of the shortfalls of current gold standard antenatal therapy for FNAIT.

Mouse models

Human platelet antigens are unique to the human system but mouse models have now emerged that allow investigation of the effects *in vivo* of novel antibody therapies for anti-HPA-1a-driven FNAIT and of potential prophylactic therapies to prevent alloimmunization.

The first of these models uses β3(-/-) mice transplanted with littermate bone marrow transduced with a lentivirus vector containing the human β3 gene *ITGB3* encoding either leucine-33 (HPA-1a) or proline-33 (HPA-1b) under the control of the *ITGA2B* promoter. Transplanted mice express a hybrid murine/human αIIbβ3 complex on the platelet surface[72] but, crucially, this complex bears the corresponding HPA-1a or -1b antigen making the mice suitable for studying the effects of natural and recombinant human HPA-1a antibodies on platelet survival *in vivo*.[73]

Another model, developed by Ni *et al*., relies on the formation of isotypic antibodies in either β3-/- or GPIbα-/- mice which are immunized either against human or mouse platelets that bear these receptors.[74,75] The animals form polyclonal antibodies that can trigger platelet destruction. Crucially, immunized pregnant mice can be bred with wild-type males, therefore generating pups expressing these platelet receptors. These pups exhibit all the signs of FNAIT with thrombocytopenia and hemorrhages although, interestingly, the rate of miscarriage was far greater in the GPIbα-immunized group, hinting at a different disease process. These models have been used not only to analyze the effect of IVIg (showing a clear amelioration of the disease), but also in proof-of-principle studies using FcRn blockade (see below).

HPA-1a blocking antibodies

The binding site for polyclonal HPA-1a antibodies is limited to a finite number of epitopes on the β3 integrin, with leucine-33 being a critical residue.[76] It should, therefore, be possible to generate an HPA-1a-specific therapeutic IgG antibody of sufficient affinity to block maternal antibodies to the HPA-1a epitope. Modifications could be made to the constant region to render the antibody non-destructive but preserve its half-life and transport across the placenta via the FcRn receptor, thereby removing the need for risky intra-uterine procedures. In essence, women who are alloimmunized and at high risk of FMAIT could be treated by regular intravenous injections of a recombinant antibody that would cross the placenta and compete with maternal HPA-1a antibodies in binding to the fetal platelets with the aim of raising the fetal platelet count to prevent serious *in utero* and perinatal bleeding (Figure 1).

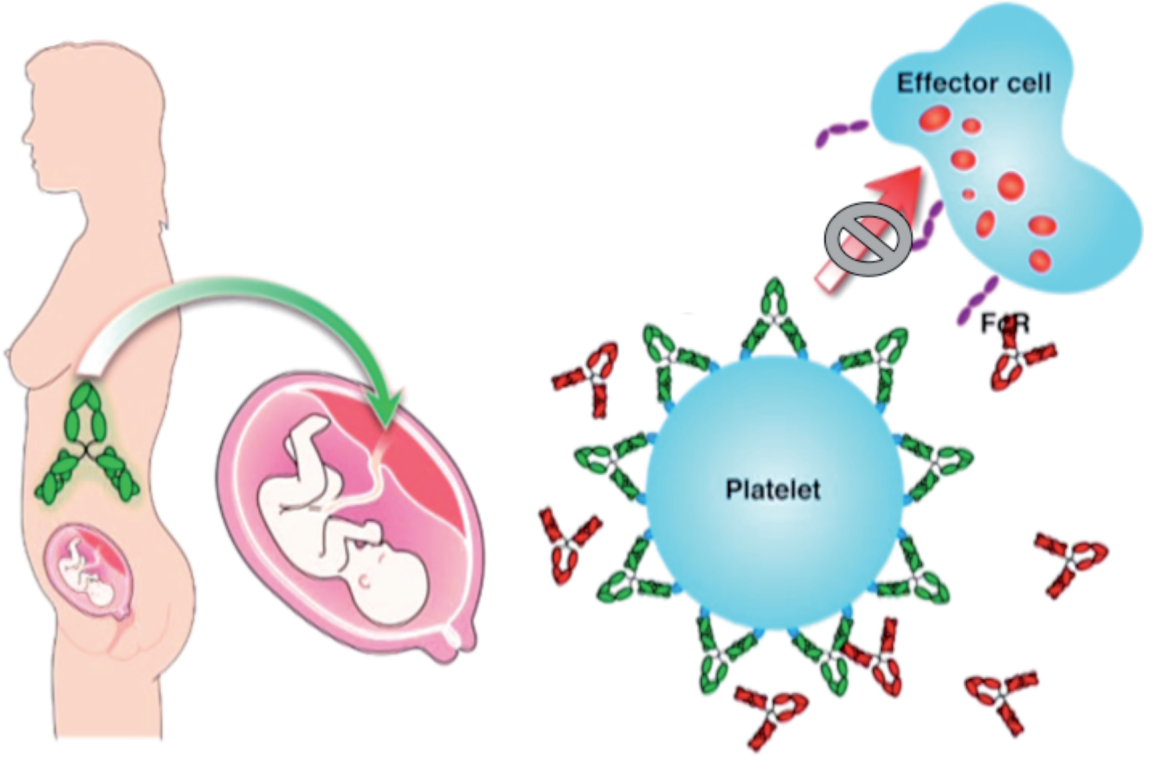

Figure 1. Blocking antibodies for antenatal treatment of fetal and neonatal alloimmune thrombocytopenia. Therapeutic recombinant antibodies (in green) are administered to the pregnant mother who is alloimmunized against HPA-1a. The recombinant antibodies cross the placenta into the fetal circulation. The affinity of the therapeutic compound for the HPA-1a epitope is such that it outcompetes the maternal polyclonal destructive antibodies (in red). The therapeutic antibodies have a modified constant region that does not bind to the Fc receptors on macrophages, therefore preventing platelet destruction.

Two groups have focused on this strategy. Ghevaert *et al*. used a recombinant antibody with a variable domain antibody fragment of nanomolar affinity ($K_d = 6\times10^{-8}$ M) for HPA-1a generated from the maternal B cells of an FMAIT case by phage display.[77] The recombinant human IgG1 antibody (B2G1, also sometimes described as CamTran) derived from this fragment was shown to be sufficiently specific for HPA-1a to permit its use as a routine phenotyping reagent.[78] Crucially, *in vitro* studies showed that B2G1 was of sufficient affinity to block binding of maternal polyclonal HPA-1a antibodies from 18 cases of FMAIT to fetal HPA-1a1b platelets by 70%-95%.[73] Importantly, the binding of B2G1 to HPA-1a1b platelets did not affect their function in a range of *in vitro* assays.[79] To generate the non-destructive constant region whilst preserving the half-life and transplacental transport capabilities of a human IgG1 antibody, residues from human IgG2 and IgG4 were substituted into regions of the IgG1 CH2 domain involved in binding to human FcγRI-III.[80] *In vitro* studies have shown that the monocyte chemiluminescence (MCL) response to HPA-1a1b platelets sensitized with this antibody, B2G1Δnab, is only 15% of that observed with B2G1. Crucially, in competition assays, B2G1Δnab reduced MCL response to platelets sensitized with 18 different maternal sera containing HPA-1a antibodies by more than 75%.

Using the chimeric mouse model described above, in which mouse platelets express the human HPA-1a epitope, Ghevaert *et al*. confirmed that platelet destruction of HPA-1a positive platelets by human polyclonal anti-HPA-1a could be prevented by the use of this recombinant antibody.[73] They went on to carry out a first-in-man study using clinical-grade antibodies.[81] Briefly, HPA1a1b platelets were isolated from healthy volunteers and sensitized *ex vivo* with either B2G1, B2G1Δnab or different ratios of these 2 antibodies. After radiolabeling the platelets were re-injected into the volunteers and platelet survival assessed through serial samplings and gamma counting. Platelets sensitized with the destructive B2G1 were removed within 2 h from circulation, whilst platelets sensitized with B2G1Δnab showed a survival similar to that of unsensitized platelets, showing the "inert" nature of the modified constant region in the human system. Crucially, when platelets were coated with different ratios of these 2 antibodies (mimicking what would be expected if B2G1Δnab was used in alloimmunized women), although platelet destruction was still observed, survival was prolonged to a point where B2G1Δnab could potentially induce a clinically useful rise in the fetal platelet count to a "safe" level ($>50\times10^9$/L).

A similar approach has been used by Bakchoul *et al*., but instead of modifying amino acid residues to make a non-destructive antibody, they deglycosylated the antibody Fc region using endoglycosidase F. Removal of N-glycan inhibits recognition of the Fc portion of the antibody by FcR(receptors)[82] whilst preserving binding to the FcRn,[83] thereby allowing transplacental transport. Using the murine monoclonal antibody SZ21, they first demonstrated that an $F(ab)'_2$ fragment (which lacks the Fc region necessary for binding to FcRs) was able to block platelet clearance by maternal HPA-1a alloantibodies in a murine model.[84] They went on to demonstrate a similar effect using the deglycosylated version of SZ21.[85] Although the data support the principle of using deglycosylated antibodies in this setting, SZ21 can bind to the HPA-1b epitope at high concentration which would potentially preclude its administration to HPA1b1b women. In addition, use of a murine antibody for human therapy raises the risk of antibody formation against the therapeutic compound.

Although the results with blocking antibodies are promising, this approach raises numerous questions (discussed by Ghevaert *et al*.[73]). In particular, how effective will the *in vivo* placental transport be, given that the HPA-1a epitope is expressed on the placenta? What concentration of antibody should be used, and should it be tailored to the affinity of the maternal antibodies? And how would we monitor response to therapy?

FcRn blockade

The neonatal Fc receptor (FcRn) is a heterodimer consisting of a β2-microglobulin and a transmembrane α-chain that is homologous to the α-chain of major histocompatibility complex class I. IgG binding to FcRn is pH-dependent, with binding occurring at low pH. FcRn plays an important role in extending IgG half-life in the circulation[86] and in the active transplacental transport of IgGs from the mother to the fetus during pregnancy.[87] The potential of FcRn blockade as a means of treatment for FNAIT was first demonstrated in a murine model where β3-/- mice were cross-bred with FcRn-/- animals. The β3-/- females were immunized and bred with wild-type males as described above, but FNAIT was only observed in the β3-/- FcRn+/+ pregnant females whilst β3-/- FcRn-/- showed no pathology in the pups.[88] Using the GPIbα-/- mouse model described above, the authors went on to demonstrate that FcRn blockade with a monoclonal antibody reduced the rate of miscarriage and thrombocytopenia in GPIbα-/- immunized pregnant females, reproducing the beneficial effect of IVIg.[75] The obvious advantage of this approach compared to the blocking antibodies is that it can be applied to all pregnancies at risk of FNAIT, regardless of maternal antibody specificity.

Screening

The screening of all pregnant women to detect pregnancies at risk of FNAIT has not been adopted in most countries. This is due to two main facts making FNAIT an altogether different proposition compared to HDN due to anti-D. First, there is a lack of consensus on the best antenatal treatment strategy for affected fetuses, as discussed above, and second, there is a lack of reliable non-invasive prognostic markers which would indicate which pregnancies would most benefit from intervention.[89] However, a large screening study undertaken in Norway of over 100,000 thousand pregnancies, which entered all HPA-1a alloimmunized pregnancies into a dedicated care pathway, uncovered some interesting facts. All alloimmunized women were offered a Caesarean section at 36 weeks of pregnancy with antigen-negative platelets available to the newborn if severe thrombocytopenia was detected at birth. In itself this led to a reduction of morbidity and mortality compared to other published series.[18] Cost-effectiveness calculation for this strategy generated over 200 Quality-Adjusted Life Years (QALYS) among 100,000 women with a reduction in healthcare costs by approximately €1.7 million compared to a non-screening strategy.[90] These costs are somewhat lower than previously estimated

in albeit much smaller studies,[31,91] but still within the threshold of generally acceptable healthcare costs (roughly €30,000-€50,000 per QALY). Interestingly, a comparison of the rate of detection of FNAIT cases between a screened population in Norway *versus* the observed FNAIT rate in the non-screened population in the same country (where FNAIT was diagnosed on the basis of symptomatic referral) shows that 85% of cases would go unnoticed without screening.[92] In support of these results, a retrospective study carried out in the UK showed that cases where the diagnosis of FNAIT was unknown prior to delivery were more likely to experience ICH (20% *vs*. 4%) when compared to cases where the diagnosis was made and some form of antenatal management put in place.[54]

The debate is far from being settled when it comes to predicting outcome. The only universally agreed predictive factor is the outcome of FNAIT in the previous pregnancy. Retrospective studies of cases that were detected clinically have generally shown no correlation between *in vitro* assays looking at antibody titer and/or chemiluminescence activity and outcome[93,94] whilst prospective studies have shown the opposite.[18,19] A French study using serial samples collected throughout the pregnancy whilst on therapy (IVIg) showed that an antibody cut-off level could be implemented in order to determine treatment success or failure without the need for invasive fetal sampling.[95,96]

Prophylaxis

Since prospective studies show that a significant number of women are alloimmunized against HPAs around the time of birth, this has raised the question of the potential benefit of prophylactic treatment in order to prevent alloimmunization. The principle is to use IgG antibodies directed against fetal epitopes in order to inhibit the maternal immune response (a process called antibody-mediated immune suppression, AMIS).[97] Although the mechanism leading to AMIS is still unknown, the widely-used anti-D program to prevent HDN is one of the most successful immunotherapies to have hit the clinic in the last century. The first proof of principle study of this approach in FNAIT was carried out in the β3-/- mouse model. Administration of anti-β3 murine sera prevented alloimmunization against transfused β3+ platelets. In a similar vein, polyclonal human anti-HPA-1a Ig prevented alloimmunization after transfusion of HPA-1a positive platelets in β3-/- mice.[98] Crucially, prophylaxis was shown to prevent FNAIT in the pups of female β3-/- which were transfused with β3+ platelets. Based on these encouraging results, a European Union-funded consortium is now looking at the potential prevention of perinatal alloimmunization in HPA-1a negative women using a polyclonal donor-derived HPA-1a antibody preparation.[99] The effective clearance of HPA-1a positive platelets using the recombinant IgG1 HPA-1a antibody B2G1 shown by Ghevaert *et al*., raises the possibility of using such recombinant antibodies for prophylaxis.[81]

Conclusions

FNAIT remains a serious condition which has been described as a "rare disease" but is in fact more frequent than other disorders that are currently being screened for in pregnant women/newborns (such as anti-D HDN, phenylketonuria, etc). Numerous questions remain, in particular how to identify the high-risk cases and what treatment regimen to put in place in the antenatal period. However, the last eight years has opened the door to novel approaches: universal screening, new therapies and the potential of a prophylactic strategy. I have no doubt that the next eight years will yield results that will ensure significant progress in our understanding and management of FNAIT.

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