with WT CAR T cells in combination with soluble CV1 and rituximab (59 days) or CV1 plus rituximab (47 days). These experiments clearly demonstrated the synergistic therapeutic effects of CAR T cells and mAb therapy, which was further enhanced by Orexi CAR T-cell secretion of CV1. These effects were suggested to be due to increased ADCP activity, as in vivo depletion of macrophages with clodronate abrogated the therapeutic effect of rituximab treatment in the tumor-engrafted NSG mice. In addition, in vitro cellular coculture experiments were performed with anti-inflammatory M2 macrophages and CAR T cells, which suggested that Orexi CAR T cells may decrease the levels of immunosuppressive IL-10 and increase the levels of interferon gamma, compared with WT CAR T cells. This suggests that Orexi CAR T cells are able to reverse the immunosuppression of M2 macrophages, thereby enhancing immune activation and tumor cell lysis. The murine in vivo experiments were performed in the intraperitoneal cavity, which is enriched in macrophages, supporting ADCP. Additional experiments, however, are required to assess the precise contribution of ADCP, ADCC, and CDC in a more typical in vivo setting, as NSG mice are deficient in mature lymphocytes and natural killer cells and are relatively deficient in complement.

In summary, Dacek et al report a potential breakthrough in the field by presenting a novel strategy to enhance the efficacy of therapeutic mAb cancer immunotherapy by addition of Orexi CAR T cells, which locally secrete the CD47-SIRPα checkpoint blocker CV1, which upends the immunosuppressive tumor microenvironment by enabling macrophage ADCP/ADCC (see figure). More importantly, the strategy of local secretion of CV1 bypasses the CD47 sink present on all cells in the body and may, thereby, prevent systemic toxicities. Further preclinical validation is warranted, followed by clinical trials investigating this exciting and promising approach, which has the potential to overcome the limitations of monotherapy, thereby preventing therapy refractoriness and disease relapse.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Fattizzo et al, page 2016

Love's labor's lost? Fetal vs maternal AIHA outcomes

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In this issue of *Blood*, Fattizzo et al describe the results of a multicenter cohort of patients with autoimmune hemolytic anemia (AIHA) during pregnancy that demonstrated good maternal outcomes despite severe hemolysis and substantial relapse rates but also revealed an increased rate of serious fetal and neonatal complications.[1]

Physicians caring for pregnant patients are often limited by the paucity of data. This is particularly true for conditions such as AIHA that are already rare in the general population, although rates are higher in pregnancy.[2] For the practicing hematologist, this large cohort provides much needed insight into the expected course, therapeutic options, and outcomes of AIHA in pregnancy.

Of the 20 patients with proceeding AIHA, 10 had a relapse during pregnancy. Given that the hematologists and obstetricians caring for these patients were likely monitoring for signs of hemolysis, it is noteworthy that this did not afford a window for early intervention. These cases were included in the study's median hemoglobin of 6.4 g/dL with a range of 3.1 to 8.7 g/dL for the 45 total pregnancies in 33 distinct patients, indicating even those who were being surveilled still developed severe hemolysis. In counseling patients with prior AIHA who are considering pregnancy, this provides an understanding that treatment will be required in many individuals and what such treatment is likely to entail.

In accordance with guidelines,[3] patients with both relapsed and de novo AIHA received corticosteroids as first-line therapy, and this was sufficient for most patients. Given its extensive safety record in pregnancy, it is not surprising that IV immunoglobulin (IVIG) was used as an adjunct in many cases, despite being a less effective therapy for AIHA than for other autoimmune diseases.[3] The high rate of transfusion (58%), which is unimpeachable in the setting of such severe anemia, carries both general and pregnancy-specific considerations, such as alloimmunization increasing the risk of hemolytic disease of the fetus and

newborn, which may be difficult to attribute to alloimmunization given concurrent maternal autoantibodies. Corticosteroids, IVIG, and transfusion were sufficient to stabilize all patients in this series, allowing other therapies to be deferred until postpartum. Rituximab, a mainstay of therapy outside of pregnancy for those without a complete response or inability to wean corticosteroids, carries a risk of prolonged neonatal lymphopenia.[4] As such, the ability to defer rituximab is likely preferable in most scenarios. However, administration during pregnancy should not be catastrophized, knowing that even in cases documenting neonatal lymphopenia, serious infection is a rarity.[4]

Venous thromboembolism (VTE) occurs at an increased rate in patients with hemolysis and is among the most common hematologic complications of pregnancy, occurring in 1.72 per 1000 deliveries.[5] None of the pregnancies in this study were complicated by VTE. A variety of strategies were used, including aspirin, heparin, and both aspirin and heparin, but two-thirds of patients were on no VTE prophylaxis. Overall, the number of pregnancies was too small to provide definitive insight into the relative incidence of VTE. As such, the consideration of VTE prophylaxis must still be individualized and should still be considered, particularly in patients with additional concurrent risk factors such as prior splenectomy.

Hematologists caring for patients who are pregnant or are considering pregnancy frequently field questions regarding not only health consequences but also impacts on fertility. This study provides the insight that early pregnancy loss, which occurred in 15% of pregnancies, did not differ appreciably from the general population.[6] It is noteworthy that 5 of 6 losses were in patients with ongoing hemolysis, although this could be due to chance alone, given the overall incidence of early losses. Although maternal complication rates during pregnancy were higher than expected, apart from AIHA itself, the complications did not endanger the life of the mother. As such, the primary maternal consideration appears to be control of hemolysis.

Unfortunately, fetal and neonatal outcomes deviated greatly from the general population. The authors report a complication rate of 22%, including intrauterine growth restriction, newborn hemolysis, respiratory distress, preterm birth, and, most alarmingly, 2 deaths. In contrast to maternal outcomes, this is sobering and merits counseling about these potentially devastating outcomes. The observational nature of the data, size of the sample, and relative uniformity of treatment strategies for hemolysis during pregnancy make an inference on how management of hemolysis impacts these outcomes impossible. However, with only partial responses in approximately one-third of patients, it is worth contemplating the role for more aggressive management of AIHA during pregnancy.

Second-line therapies are often deferred to the postpartum period even for the most severe cases, despite overall good safety data from other maternal diagnoses. This is likely appropriate if control is rapidly achieved. However, when considering the role of rituximab, the hypothetical risk of neonatal lymphopenia should be weighed against the direct, deleterious effect of hemolysis and severe anemia on the pregnancy. A false dichotomy is often constructed that puts maternal and fetal health as opposed priorities, but severe maternal anemia is highly likely to negatively impact fetal development, and maternal autoantibodies can cross the placenta and cause hemolysis in the fetus or newborn.[2] Fetal health is ultimately dependent on maternal health, not a wholly independent outcome. As such, rather than taking the treatment schema in this study as the optimal strategy, it may be best to view it as a starting point and not a reason to forgo additional therapies, if hemolysis is slow to improve or incompletely controlled.

In summary, although caution must be used with a modest sample size, given the rarity of this condition, the authors provide much needed information on the expected course of AIHA in pregnancy that aids in both preconception counseling and management of patients with AIHA relapsing or occurring de novo during pregnancy. Although this study helps fill a gap in knowledge regarding AIHA in pregnancy, many questions remain unanswered, including the optimal approach to VTE prophylaxis and how to improve fetal and neonatal outcomes.

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THROMBOSIS AND HEMOSTASIS

Comment on Ivanciu et al, page 2022

Not so fast, antithrombin!

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In this issue of *Blood*, Ivanciu et al[1] report that catalytically active zymogen forms of factor IX (FIX) were resistant to plasma inhibitors like antithrombin (AT), and they enhanced thrombin generation and clot formation in vivo.

Blood coagulation is a highly regulated process.[2] Coagulation, of course, is necessary following injury, but unrestrained coagulation can be life threatening. However, there are times when easing the restraints on coagulation would be