inside blood commentary

7 JANUARY 2016 | VOLUME 127, NUMBER 1

CLINICAL TRIALS AND OBSERVATIONS

Comment on Bride et al, page 17

Serendipity in splendid isolation: rapamycin

V. Koneti Rao NATIONAL INSTITUTES OF HEALTH

In this issue of *Blood*, Bride et al report results of the first prospective multi-institutional trial of a long-term single-agent therapy for refractory cytopenias using rapamycin in 30 patients and show remarkable efficacy in children with autoimmune lymphoproliferative syndrome (ALPS).[1]

On Easter Sunday of 1772, a Dutch expedition led by Jacob Roggeveen sighted a small treeless volcanic island in the vast expanse of the southeast Pacific Ocean and named it Easter Island. That Dutch landing party and subsequent visitors to these islands, known by the locals as Rapa Nui Island, have marveled at the sight of gigantic stone figures (up to 30-feet high) of porous red rock known as moai, standing in silent rows along the shore. These statues had remained virtually isolated from the rest of humanity for a millennium. Polynesian navigators were accomplished sailors in an ancient world. Around 1500 BC, they traveled across the vast ocean guided only by stars, flight patterns of sea birds, and ocean currents; they settled every habitable island within the Polynesian triangle formed by New Zealand, Hawaii, and Easter Island. The art of Easter Island represented the supernatural power of the gods and the chiefs of the native inhabitants; enduring fascination for art historians related to oceanic folklore and sculpture art. Moai statues as exotic icons are embraced by contemporary cultures as a shared human heritage (see figure). The island's splendid isolation has also bestowed upon the humanity an immunomodulatory agent we all readily recognize today.[2] Its discoverer, Suren Sehgal, aptly named it rapamycin based on its origin from the bacteria *Streptomyces hygroscopicus* collected from the soil under 1 of the Rapa Nui Island statues by a Canadian expedition in 1972.[3] Although it was isolated and characterized initially as an antifungal antibiotic, subsequent studies, thanks to the persistent efforts of Dr Sehgal to assess it as an anticancer agent, revealed its impressive immunosuppressive activity.[4] It received US Food and Drug Administration approval for use in organ transplantation in 1999 and became more widely known by its generic name, sirolimus.[5] Elucidation of the protozoal and metazoal proteins affected by this compound led to better understanding of mechanistic target of rapamycin (mTOR) signaling pathways related to growth, proliferation, and cell death in human health and disease. The *MTOR* gene, coding for a serine/threonine kinase (http://www.ncbi.nlm.nih.gov/gene/2475), was discovered by studying rapamycin-resistant mutants of *Saccharomyces cerevisiae*. Understanding of mTOR signaling has provided the biological basis for the development of several targeted therapeutics, including many rapamycin analogs currently under investigation.[6]

Moai statues assembled from Nanoblocks by the author (V.K.R.).

The work by Bride et al in this issue illustrates the value of studying pathophysiology-based treatments of a rare genetic disease like ALPS and applying the lessons learned to more common sporadic autoimmune problems including multilineage cytopenias. Notably, sirolimus treatment of ALPS patients with massive lymphadenopathy and splenomegaly led to reversal of the disease process itself, reflected in relief of the cytopenias and normalization of the signature double-negative T cells of ALPS in all 12 patients included in the study. No metabolic or infection-related adverse events due to sirolimus were noted in children and young adults enrolled on this trial. However, it is imperative to be wary of the toxicities that may be uncovered as more individuals including adults with normal to high normal cholesterol and lipid levels are exposed to it for the long-term as modulation of lipid metabolism is a known side effect of sirolimus.[7,8] Patients with secondary multilineage cytopenias, including those due to systemic lupus erythematosus and common variable immune deficiency, were also treated with sirolimus as a long-term immunomodulatory intervention in this study, underscoring the value of sirolimus as a good steroid-sparing agent that may allow us to avoid the toxicities of long-term corticosteroids in growing children. Many ALPS patients require some immunosuppression using sirolimus,

mycophenolate mofetil, or another drug indefinitely to treat their cytopenias as their underlying genetic defect is irreversible.[9]

Long-term management of chronic and refractory cytopenias due to sequestration or autoimmune peripheral destruction has remained empirical and eluded rational evidence-based approaches. Barring some industry-sponsored trials of thrombopoietin mimetic agents in immune thrombocytopenia, there are not many recent investigator-initiated multicenter trials enrolling children or adults with autoimmune cytopenias. With the advent of cheaper and more readily accessible genetic testing, more and more "rare" disorders of lymphoproliferation and autoimmunity are being recognized. Treatment approaches learned from ALPS and many related disorders can serve as a good model to conduct multicenter trials of targeted immunomodulation vs global immunosuppression to ameliorate pathophysiology in many of these conditions with genetic underpinnings. More often these patients are children and young adults who shall require prolonged therapy with long-lasting consequences of any intervention and they benefit from diligent longitudinal follow-up by caregivers familiar with them and their underlying disease.

Treasured soil from under the remote Rapa Nui Island statues[10] in the Pacific Ocean provided us the bacteria-secreting rapamycin (sirolimus). Better understanding of the underlying pathophysiology of rare genetic diseases including ALPS offers us an opportunity to study safe and effective targeted therapeutics in collaborative multi-institutional clinical trials as exemplified by Bride et al in this issue.[1]

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

REFERENCES

1. Bride KL, Vincent T, Smith-Whitley K, et al. Sirolimus is effective in relapsed/refractory autoimmune cytopenias: results of a prospective multi-institutional trial. *Blood.* 2016;127(1):17-28.

2. Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc.* 2003;35(suppl 3):7S-14S.

3. Vézina C, Kudelski A, Sehgal SN. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J Antibiot (Tokyo).* 1975;28(10):721-726.

4. Douros J, Suffness M. New antitumor substances of natural origin. *Cancer Treat Rev.* 1981;8(1):63-87.

5. Sehgal SN. Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem.* 1998;31(5):335-340.

6. Seto B. Rapamycin and mTOR: a serendipitous discovery and implications for breast cancer. *Clin Transl Med.* 2012;1(1):29.

7. Elloso MM, Azrolan N, Sehgal SN, et al. Protective effect of the immunosuppressant sirolimus against aortic atherosclerosis in apo E-deficient mice. *Am J Transplant.* 2003;3(5):562-569.

8. Moraitis AG, Freeman LA, Shamburek RD, et al. Elevated interleukin-10: a new cause of dyslipidemia leading to severe HDL deficiency. *J Clin Lipidol.* 2015;9(1):81-90.

9. Rao VK. Approaches to managing autoimmune cytopenias in novel immunological disorders with genetic underpinnings like autoimmune lymphoproliferative syndrome. *Front Pediatr.* 2015;3:65.

10. Kjellgren E. Introduction. Splendid Isolation: Art of Easter Island. New York, NY: Metropolitan Museum of Art; 2001:11-23.

DOI 10.1182/blood-2015-11-679829

● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Byrd et al, page 79

Obinutuzumab: the more the merrier?

Jan A. Burger THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

In this issue of *Blood*, Byrd et al present data from a randomized phase 2 study in which 78 previously untreated patients with chronic lymphocytic leukemia (CLL) received 8 cycles of either 1000 mg (the current standard dose) or 2000 mg of the anti-CD20 monoclonal antibody (mAb) obinutuzumab.[1] The authors report a higher overall response rate with higher doses of obinutuzumab (67% vs 49%), but there was no significant difference in progression-free survival (PFS) between groups.

Obinutuzumab (GA101) is a novel type 2 humanized anti-CD20 mAb that was glycoengineered to reduce attachment of fucose residues to the crystallizable fragment (Fc) portion of the mAb. This enhances the affinity of the antibody for binding to Fcγ receptors of the IIIA subgroup (FcγRIIIA or CD16a) on effector cells, thus improving antibody-dependent cell-mediated cytotoxicity (ADCC). Being a type 2 antibody, obinutuzumab mostly relies on ADCC and direct cytotoxic effects. In contrast, type 1 antibodies (rituximab and ofatumumab) display stronger complement-dependent cytotoxicity, less ADCC, and minimal direct cytotoxicity.

Over the past 2 decades, anti-CD20 mAbs have become a cornerstone of therapies for patients with B-cell malignancies, including CLL. As a single agent, rituximab was initially perceived as a relatively inactive agent in CLL, with response rates ranging between 5% and 14%. The characteristic low CD20 expression, which distinguishes CLL from other mature B-cell malignancies, presumably contributes to these relatively low response rates. However, more dose-dense[2] or higher-dose regimens[3] increased the response rates to single-agent rituximab and invigorated the interest in treating CLL patients with CD20 mAbs. The most established use of anti-CD20 mAbs in CLL is as a partner in chemoimmunotherapy (CIT) regimens combined with conventional agents. In these combinations, anti-CD20 mAbs improved PFS and overall survival when added to fludarabine and cyclophosphamide,[4,5] bendamustine,[6] or chlorambucil.[7,8] Furthermore, single-agent anti-CD20 mAbs are commonly used (especially in the United States) in CLL patients who are unfit for chemotherapy-based regimens because of advanced age and/or poor performance status.

The data presented by Byrd et al[1] demonstrate that obinutuzumab as a single agent can induce complete remissions in 5% of CLL patients treated with standard-dose and in 20% of patients treated with higher-dose obinutuzumab, an indicator of the high efficacy of obinutuzumab, which was highlighted in the pivotal trial.[7] On the basis of these data, one could speculate that obinutuzumab, currently approved for use in combination with chlorambucil for untreated CLL patients who are unfit to undergo CIT, will increasingly be used as a single agent. The data clearly corroborate that obinutuzumab has high single-agent activity, but they do not definitively answer what dose is optimal or