What We Know and Do Not Know About Chronic Pain in Adults With Sickle Cell Disease


The current opioid epidemic presents unique challenges for adults with sickle cell disease (SCD) and the providers who care for them. Given the public discourse about opioid misuse, health care providers for children and adults with SCD must be especially cognizant of their prescribing practices and emerging state-based opioid regulations that may impact management of acute and chronic pain in children and adults with SCD.

For decades, a disproportionate number of physicians and nurses have harbored negative attitudes about pain management in adults with SCD. In one study, 53 percent of emergency department physicians and 23 percent of hematologists surveyed thought that more than 30 percent of adults with SCD have opioid abuse syndrome. Similarly, 63 percent of nurses surveyed believed opioid abuse syndrome was common in the adult SCD population, and 30 percent were reluctant to give the recommended dose of opioids upon evaluation. The consequences of this systemic bias is undertreatment of pain for many adults with SCD.

Fortunately, health care provider attitudes about pain management are not immutable. A Johns Hopkins eight-minute video serves as an educational resource for health care providers focused on general challenges of pain management and the patient’s perspective of acute pain management in patients with SCD. Viewing this short video improved health care provider attitudes about treating pain in adults with SCD using standard care guidelines.4

Dr. Joshua J. Field highlighted the five lessons for management of pain in adults with SCD. These lessons are: 1) Focus on adults with high rates of resource use for pain; 2) Treat underlying causes of pain, including SCD, aggressively; 3) apply principles of chronic pain management to a clinic model; 4) understand that higher doses and larger quantities of oral opioids often do not help; and 5) realize that parenteral opioids are not the optimal treatment of chronic pain. These lessons highlight the challenges of managing pain in adults with SCD and provide clear strategies for assessment of common problems.

Missing from the lessons learned is the significant overlap between chronic pain and depression and the role of the primary care provider. In a recent review, individuals with SCD and depression had almost a three times greater relative risk of being high–health care utilizers and 50 percent greater rates of hospitalization (2.9 vs. 1.8 hospitalizations per year) when compared with individuals without depression. The optimal management of depression in adults with SCD is not known. However, the presence of depression, a common and potentially modifiable risk factor in adults with SCD, warrants further evaluation. If adults with SCD do not have primary care providers, then the adult hematologist or health care provider is compelled to ensure that the shared strategies for management of chronic pain in the general population are included in the treatment of adults with SCD.

As Dr. Field points out in his article, there is a paucity of evidence in management of acute and chronic pain, and even less evidence as to the modifiable risk factors driving chronic pain and optimal strategies for its management. Key to Dr. Field’s approach is a trusting relationship between the patient and the provider, coupled with a stepwise approach for increased intensity in medical management of chronic pain. Specifically, if the patient averages at least one episode of pain per month and is on a maximum-tolerated dose of hydroxyurea therapy, then regular blood transfusion therapy is offered to decrease the maximum hemoglobin S concentration to less than 50 percent. If this approach does not abate the frequency of admissions for acute pain and the hemoglobin S concentration is kept to less than 50 percent, then Dr. Field recommends erythrocytapheresis with a goal of keeping the maximum hemoglobin S concentration significantly lower than 50 percent.

Is there a randomized controlled trial to support Dr. Field’s practical strategy of managing recurrent severe acute pain episodes in adults with SCD? No. However, all interventions do not require randomized controlled trials when the evidence is overwhelmingly positive and the benefits clearly outweigh the risks. Even after hematopoietic stem cell transplantation, individuals cured of SCD can have residual chronic pain syndrome for a prolonged duration after complete engraftment of donor cells. Thus, regular blood transfusions are not expected to be the definitive cure for chronic pain, but in a subset of patients, they decrease the frequency and intensity of pain episodes. Clearly more investigation is required to develop a rational approach to prevent and treat chronic pain.

What are hematologists and other health care providers to do when the most common problem affecting 50 percent of adults with SCD, recurrent severe pain, is not part of the private or public funding agencies’ research agendas? We use the strategy that Dr. Field has described, which is less than optimal, but pragmatic, compassionate, and carefully crafted to address the pressing needs of our patients and their families.

2. Dr. Michael B. Jordan

MICHAEL DEBAUN, MD, MPH
Dr. DeBaun indicated no conflicts of interest.
In a Global State of Mind

As the Highlights of ASH meetings in Asia-Pacific and Latin America take place in March and April, respectively, the timing seems appropriate to consider the efforts that we make as a global Society to help hematologists treat difficult diseases at home and abroad. In many ways, ASH’s global reach is a powerful reflection of the Society’s mission to promote research, clinical care, education, training, and advocacy in hematology, regardless of international borders, and involves not only major meetings such as Highlights of ASH, but also our publications, awards, and other initiatives that promote diversity, education, and training. As programs expand and new initiatives are developed, the Society’s outreach becomes even more imperative to ensure that we keep our domestic and international members informed about the broadening mix of ASH programs and services.

You can learn about the entire growing roster of programs and awards that define our international efforts at www.hematology.org/Global. For this column, I want to shed a spotlight a few of the initiatives that provide a real flavor for what ASH seeks to achieve worldwide. At the annual meeting you may have had the chance to visit the Global Capacity-Building Showcase in the poster hall. This new poster category was designed to highlight extraordinary initiatives in low- and middle-income countries to address local challenges in hematology research or care delivery that highlight existing partnerships with measurable outcomes. And ASH’s support for global capacity-building extends beyond any single event: numerous initiatives have been created with the goal of helping to develop knowledge, disease management, clinical and research skills, and improved outcomes.

The Visitor Training Program (VTP) is another program that fosters outreach and capacity-building by funding hematology professionals from low- and middle-income countries to train in a specific area of hematology with an ASH member for up to 12 weeks. Training can focus on skills either in the clinic or in a research or laboratory setting, and is intensive enough such that in the timeframe provided, participants can start implementing what they’ve learned upon return to their home institutions and start having an impact on hematologic patient care. Last year, ASH awarded 25 VTP grants to participants from 13 countries including Argentina, Azerbaijan, Bangladesh, Egypt, Georgia, India, Malaysia, Myanmar, Nigeria, Pakistan, Peru, Sri Lanka, and Turkey.

Supporting the careers of future leaders in the field is a clear priority for ASH. Feedback from members was a big stimulus for creating the Global Research Award in 2017. This award is for hematologists outside of North America who are between the completion of training and the establishment of their independent careers. The number and quality of applications in the inaugural has been impressive. We encourage all eligible international ASH members with an MD, PhD, MD-PhD (or its equivalent) to learn more about this opportunity and to submit a letter of interest before August 31, 2018 (www.hematology.org/Global/Research).

Through Health Volunteers Overseas (HVO), members of ASH share expertise with their counterparts working at institutions in low- to middle-income countries. Local hematologists at program sites in Cambodia, Peru, and Tanzania have had the opportunity to present their needs, both in the clinic and the laboratory, that are addressed by volunteers through a variety of consultative activities including mentorship, lectures, teaching materials, and other activities. In 2017, ASH facilitated placement of 12 volunteers at the active HVO sites.

I’ll close by noting that this Year of the Dog marks ASH’s 60th annual meeting. It is fitting to observe this milestone not only by acknowledging the breakthroughs that we have achieved as a field, but also celebrating the drivers that have made these innovations possible: clinicians and scientists who call all corners of the world “home.” They truly represent the “Best of ASH.” With the help and participation of ASH’s membership, I look forward to seeing continued growth in our body of programs and offerings to impact blood disorders around the globe.

Sincerely,

Alexis A. Thompson, MD, MEI

Ash Medical Educators Institute

(Cont. from page 1)

Dr. Annie Im is an assistant professor of medicine in the Division of Hematology/Oncology at the University of Pittsburgh who participated in last year’s MEI and was in a similar situation as Dr. Mandernach. “I had just been offered the opportunity to become program director of our hematology/oncology fellowship program,” she said, “and I was hoping that MEI would provide an opportunity to meet mentors and colleagues in medical education. I was also hoping to find a forum to discuss some of the challenges of a medical education career.”

Dr. Mandernach and I say that they benefited from both the formal curriculum and also the more informal networking and mentorship aspects of MEI. “I had worked with educational mentors and colleagues in other specialties, but this was the first time that I had seen such an emphasis on medical education in hematology,” said Dr. Im. “We also had small groups where we refined our educational scholarly projects, which helped me with my project and also was a lot of fun. My small group still keeps in touch regularly.”

“It was very clear the faculty were dedicated to sharing their experiences in medical education, as well as mentoring the participants,” added Dr. Mandernach. Her scholarly project, which got its start at the MEI, has rolled out in pilot form for the adult hematology/oncology fellows caring for patients with sickle cell disease. It will soon expand to pediatric hematology/oncology fellows, internal medicine residents, and family medicine residents.

The application cycle for the 2018 workshop is underway, with applications due March 30. MEI is open to senior fellows and faculty of any level who see medical education as a major part of their professional roles.

“It was invigorating to be involved with a group of like-minded individuals who were excited about medical education,” Dr. Mandernach summarizes. “Simply put, the program was fantastic.”

For additional information and to apply before March 30, visit www.hematology.org/MEI
Upcoming ASH Awards Deadlines

ASH is committed to supporting hematologists in all stages of their careers and thus provides an array of awards and programs to help them advance in the field of hematology. Several application deadlines are coming up; make sure to check the ASH website for more information.

- The Harold Amos Medical Faculty Development Program (ASH-AMFDP), part of the Minority Recruitment Initiative, provides four years of research support, including an annual stipend of up to $75,000 and an annual grant of $30,000 to support research activities for underrepresented minority scholars in hematology. Make sure to apply by March 15, 2018, via www.hematology.org/ASH-AMFDP.

- The ASH Bridge Grant helps hematologists continue their research amidst severe National Institutes of Health (NIH) funding reductions. A $150,000 award is granted to an ASH member who applied for an NIH R01 grant or equivalent but was denied funding due to budget outcawks. ASH awards approximately 20 to 30 one-year awards each year. For additional information and to apply by May 1, 2018, visit www.hematology.org/BridgeGrants, and be sure to read the article about the history of the Bridge Grant on page 7 of this issue.

- The ASH Clinical Research Training Institute (CRTI) is a yearlong education and mentoring program for hematology fellows and junior faculty at academic medical centers. CRTI participants will have the opportunity to learn about clinical research methods, research collaborations, statistical analysis, and managing the demands of family and career. For more information and to apply by the deadline of March 23, 2018, visit www.hematology.org/CRTI.

- The ASH Latin American Training Program (LATP) looks to help build hematology capacity in Latin America providing funding for hematologists or hematology-related health care professionals in the region. LATP offers up to 12 weeks of training in areas including flow cytometry and molecular biology, adult stem cell transplantation, and thrombosis and hemostasis, among others. For further details and to apply, go to www.hematology.org/LATP. The application deadline is March 4, 2018.

- The ASH Medical Educators Institute (MEI) will be accepting 20 participants in 2018. MEI offers a "boot camp" in teaching techniques, medical education scholarship, and career development for hematologists and fellows starting medical education careers. For application requirements and to apply by the deadline of March 30, 2018, visit www.hematology.org/MEI.

- The ASH Visitor Training Program (VTP) provides funding for hematologists or hematology-related health care professionals in the developing world to receive training on a specific topic for up to 12 weeks, in an effort to help build hematology capacity in developing countries. Apply by April 6, 2018, via www.hematology.org/VTP.

- The Society’s newest award, the ASH Global Research Award, is designed to support future international scientific leaders, increase hematology capacity, and nurture global collaboration. For more information and details on how to apply, visit www.hematology.org/Global-Research. Make sure to apply by April 15, 2018.

ASH Summit on Emerging Immunotherapies for Hematologic Diseases

This new ASH meeting is taking place July 12-13, 2018, at the Omni Shoreham Hotel in Washington, DC. It will examine preclinical and clinical factors influencing the effective development, regulation, and implementation of immunotherapies for hematologic diseases. Attendees will have the opportunity to network with experts, regulatory scientists, industry, and other stakeholders, as well as earn CME and MOC credits. For more information about attending, visit www.hematology.org/immunotherapies and make sure to turn to the article on page 13 of this issue of The Hematologist.

ASH Biosimilars Webinar Series

As biosimilars’ relevance grows in the field of hematology, a newly available webinar series addresses concerns from health care providers about their use. The webinars look to increase clinical awareness, knowledge, and confidence regarding the role of biosimilars in clinical care, which can have a positive impact on patient access to biologic therapy and cost of care. Participants can experience a two-part audio-guided series including didactic learning sessions by experts and three case-based scenarios showing the use of biosimilars. To view the webinars, visit http://programs.asahcacademy.org/biosimilars/.

Still Time to Attend the 2018 International Highlights of ASH

There is still time to register and attend a 2018 Highlights of ASH meeting! Attendees of these two international Highlights of ASH meetings will obtain a synopsis by internationally acclaimed experts of the top hematology research presented at the latest ASH annual meeting and learn ways to improve patient management and care strategies. The meetings also provide an opportunity to network with top minds in the field and are designed to provide a great educational experience for hematologist, oncologists, fellows and trainees, allied health professionals, and hematopathologists. Highlights of ASH in Asia Pacific will take place March 9-10, 2018, at the Bali Nusa Dua Convention Center in Bali, Indonesia, and Highlights of ASH in Latin American will take place April 27-28, 2018, at the Windsor Convention & Expo Center – Barra de Tijuca in Rio de Janeiro, Brazil. For additional information and to register, visit www.hematology.org/Highlights.

2018 Meeting on Lymphoma Biology

Established in 2014, the ASH Meeting on Lymphoma Biology brings together experts from all over the world to discuss the latest lymphoma fundamental science, address current challenges in the field, establish the highest priorities for investigation, and develop new therapies. Laboratory-based and translational investigators, junior faculty and trainees, policy-makers, biopharmaceutical industry, and other health professionals are welcome to attend. This meeting, taking place August 2-5, 2018, at the Westfields Merriot in Chantilly, Virginia, is also a great opportunity for attendees to network with top minds in the field and earn CME and MOC credits. For additional information, visit www.hematology.org/lymphoma-biology.

Comparison of Analytical Data

<table>
<thead>
<tr>
<th>Structural Analyses</th>
<th>Functional Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary structures</td>
<td>In vitro</td>
</tr>
<tr>
<td>(as sequence)</td>
<td>- Biological assays</td>
</tr>
<tr>
<td>Higher order structures (including aggregation)</td>
<td>- Binding assays</td>
</tr>
<tr>
<td>Enzymatic post-translational modifications (such as glycosylation, phosphorylation)</td>
<td>- Enzyme kinetics</td>
</tr>
<tr>
<td>Other variations, modifications</td>
<td>- In vivo</td>
</tr>
<tr>
<td></td>
<td>- Animal models of disease</td>
</tr>
</tbody>
</table>

FDA Criteria for Biosimilar Approval

In this webinar, Dr. Jeffrey Crawford presents the U.S. Food and Drug Administration (FDA) approval process for biosimilars, including the step-wise, "overall of evidence" approach.
The Case
A 51-year-old man with acute myeloid leukemia (AML) and unfavorable-risk cytogenetics attained a first complete remission using conventional induction chemotherapy. He has an HLA-matched related donor (his brother) who agrees to donate hematopoietic cells for an allogeneic transplant. Both the patient and donor are cytomegalovirus (CMV) seropositive.

The Question
What is the optimal approach to prevent CMV infection in patients undergoing allogeneic hematopoietic cell transplantation (AHCT) in 2018?

The Response

Can the negative effect of being a CMV-seropositive transplant recipient be overcome? The logical solution would be to use an effective antiviral prophylaxis similar to the successful strategies for preventing herpes simplex virus and varicella-zoster virus. However, there is no clear indication of the need for CMV replication itself or is there a different mechanism? Support for the theory that viral replication is bad for the patient was presented in an article by Dr. Margaret L. Green and colleagues using a retrospective cohort of patients for whom monitoring had been performed using plasma-based PCR. They found that CMV replication was associated with an increased risk for overall and all-cause mortality independent of the use of preemptive therapy. Furthermore, the risks increased with increasing viral load. Thus, it would be logical to prevent CMV replication rather than wait for it to develop and then intervene with preemptive antiviral therapy.

What are the options for preventing CMV replication? Until now, the two most effective antiviral agents have been IV ganciclovir and foscarnet. The use of both drugs, however, has been hampered by the considerable adverse effects. In a prospective, randomized-controlled study, ganciclovir use reduced the risk for CMV disease but failed to improve OS and was associated with neutropenia and bacterial infections. As a result, ganciclovir prophylaxis therapy has been limited. No controlled study has been performed with foscarnet — an agent known to cause marked serum electrolyte abnormalities. Other well-studied prophylactic approaches have included high-dose intravenous acyclovir, oral valaciclovir, and intravenous globulin; all agents have been regarded as having low efficacy. Furthermore, in a recent retrospective study examining the intensity of anti-CMV prophylaxis in haploidentical transplant recipients, less potent regimens were associated with earlier onset and an increased incidence of CMV reactivation. Therefore, interest has been directed toward the study of new antiviral drugs and anti-infective vaccines. Despite initially promising results in phase II studies, two new antiviral agents and one vaccine failed in the pivotal phase III studies. In a randomized, placebo-controlled study, maribavir failed to meet the primary endpoint of reducing CMV disease; this agent is being studied now in much higher dosages for the treatment of resistant or refractory CMV infections. An investigation using intravenous brincidofovir also was unsuccessful, the primary endpoint of lowering clinically significant CMV infection (and the need for preemptive therapy) in a randomized, placebo-controlled study was not met, and treatment was associated with significant toxicity.

Finally, recently released results of a randomized phase III study using the anti-CMV vaccine AS0113 showed inability to meet the primary and secondary endpoints.

On the other hand, letermovir is a highly specific antiviral agent against human CMV that possesses a unique mechanism of action by inhibiting the CMV terminase complex, Dr. Francisco M. Marty and colleagues recently reported the results from a randomized, placebo-controlled, phase III clinical trial conducted in CMV-seropositive AHCT recipients in which letermovir was administered through a randomized, placebo-controlled study. A total of 495 patients had undetectable CMV DNA at randomization. Only 37.5 percent of patients (122 of 325) given letermovir prophylaxis had clinically significant CMV infection or a primary endpoint event by week 24 after AHCT, compared with 60.6 percent of the placebo group (103 of 170; p=0.001). Overall, the frequency and severity of adverse events in the two groups were similar. At 48 weeks after AHCT, all-cause mortality was 20.9 percent among letermovir recipients and 25.5 percent among placebo recipients. The drug was well tolerated also, and did not demonstrate true organ toxicity including bone marrow, kidney, or liver. Both the U.S. Food and Drug Administration and the European Medicines Agency recently approved the drug based on these study results.

Will letermovir prophylaxis therapy now become the new standard of care? The study results discussed here certainly are promising, but the optimal fashion to use the drug will require additional studies. For example, it remains unclear if the 14-week duration of prophylaxis used in the study by Dr. Marty and colleagues is the optimal regimen. Although letermovir was superior to placebo in both high-risk and standard-risk patients, the risks for developing significant CMV infection after cessation of prophylaxis in the high-risk group. Such data make the case that longer prophylaxis might be beneficial. Other unknowns include the likelihood for subjects to develop CMV resistance to letermovir, though the risk was low in this study.

A more important consideration perhaps, is whether the use of an efficacious antiviral agent will increase the risk of leukemia relapse. Several reports have shown, especially in AML patients, that leukemia relapse risk is increased in the setting of CMV viremia. Other studies have not been able to demonstrate this association, including the large Center for International Blood and Marrow Transplant Registry study by Dr. Pierre Tchera and colleagues. These investigators showed that CMV replication was associated with increased transplant-related mortality and decreased OS without showing a positive effect on relapse in any disease. Although the randomized letermovir investigation did not show an effect on risk of relapse, it should be recognized that the number of patients treated was too low and the low-up too short to allow for thorough further investigation and more careful assessment of these considerations (and with more widespread use of letermovir and other effective anti-CMV agents), we might be able to answer this important question.

In addition to these issues, the economic burden of dealing with CMV infections is significant. Dr. Christine Robin and colleagues reported that the financial costs of AHCT increase by 25 to 30 percent in the setting of CMV episodes — a difference that could be reduced by appropriate use of prophylactic strategies. Given what we know today, letermovir seems to be an important development in the long-term struggle to reduce the negative effect of CMV on the outcomes of patients undergoing AHCT. However, letermovir has not been studied in children or in CMV-seronegative subjects.

Given the current approaches, we would use an antiviral prophylaxis strategy using letermovir in adult patients at high risk for CMV infection, while patients at lower risk and children could be treated using the current strategy of monitoring with quantitative PCR and preemptive antiviral therapy.

References
As this issue of *The Hematologist* went to press, Congress had just reached a deal to raise federal spending levels, paving the way for congressional leaders to finalize fiscal year (FY) 2018 budgets for federal programs such as the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC). Although the current FY officially started on October 1 of 2017, it was a series of short-term continuing resolutions (CRs) that kept government agencies funded at FY 2017 levels.

The consequences of Congress failing to fully fund the government were seen in late January when the government shut down for three days after one of the CRs expired. As part of the agreement to reopen the government, Congress passed a fourth CR to fund federal agencies and programs through February 8, 2018. This bill also included a six-year reauthorization of the Children’s Health Insurance Program (CHIP) and the suspension of certain health-related taxes, including the medical device tax, the “Cadillac” tax, and annual fees on health insurance companies. In addition to passing the CR, congressional leaders pledged to consider immigration legislation — an issue of importance for congressional Democrats.

Following a second brief shutdown during the early morning hours of February 9, Congress agreed to a deal to raise spending caps for nondiscretionary programs, including NIH, for two years, and to once again extend funding for federal agencies and programs through March 23. The bill also commits an additional $5 billion per year to NIH over the next two years, provides enhanced funding for community health centers, further extends funding for CHIP, and raises the debt ceiling. Additionally, massive cuts that had been proposed to the Prevention and Public Health Fund, which accounts for almost 12 percent of the CDC’s annual budget, have been lessened and delayed for several years. Congress must still pass an omnibus appropriations bill to fund the government for the rest of the FY, which ends on September 30.

Meanwhile, as Congress works to finalize the FY 2018 spending legislation, the president is also poised to release his budget blueprint for FY 2019 sometime in February. The president’s proposed 2019 budget is expected to be similar to last year’s, which sought to dramatically cut spending levels for most non-defense-related federal programs. ASH strongly opposed proposed cuts to programs such as NIH and CDC, as did many members of Congress, with both the House and Senate seeking increased funding for NIH. This year, the Society is dedicated to continuing its concerted advocacy efforts to increase public health and medical research funding in the FY 2019 federal budget.

While ASH continues to closely monitor the FY 2018 and 2019 budget processes, it is important for your legislators to hear from you about the need for sustained federal funding for NIH and its importance for your research and the patients you treat. Visit [www.hematology.org/Advocacy](http://www.hematology.org/Advocacy) for the latest updates and to contact your congressional delegation to help ensure that NIH and other important public health programs receive adequate funding.

### Senate Confirms New Health and Human Services Secretary

In late January, the Senate confirmed President Trump’s choice to lead the Department of Health and Human Services (HHS), Alex Azar, by a vote of 55-43. Secretary Azar replaced Tom Price, who resigned in September 2017 after a public outcry about his government travel on private planes. Secretary Azar has a long history of working in health care, having served as deputy HHS secretary under President George W. Bush and then moving on to become an executive at pharmaceutical company Eli Lilly.

Following his confirmation, ASH delivered a letter to Secretary Azar, outlining the Society’s policy priorities. The letter states ASH’s strong support for access to high-quality, affordable health care for all Americans, including access to safe and effective treatments; urges that biomedical research remain a top priority to ensure continued significant and meaningful advances in the field of hematology; and outlines the need for more federal investment in rare diseases such as sickle cell disease. ASH looks forward to serving as a resource to Secretary Azar on hemotologic issues and to working with him to address the Society’s priorities.

### ASH Submits Comments to CMS on Proposed Rule for Medicare Part D

On January 16, ASH submitted comments to the Centers for Medicare and Medicaid Services (CMS) on a proposed rule to change prescription drug policies for Medicare Part D. ASH concurred on ways that CMS could ensure access to needed medications and lower costs for patients. Specifically, the letter expressed concern about CMS’s proposal to expedite Medicare Part D plans’ ability to substitute newly approved generics for brand name drugs for patients with hematologic diseases, since all generic drugs may not be bioequivalent and since mid-year changes may disrupt patient care. Additionally, the letter noted that CMS’s proposal to shorten the days’ supply of drugs required to be provided by Part D plans to new patients transitioning from other coverage is reasonable as long as they do not result in higher costs for patients. Because of the high cost of many drugs used to treat rare hematologic diseases and cancers, the letter also expressed ASH’s support of CMS’s proposals to lower costs for patients using follow-on biological products and CMS’s proposals to lower patients’ maximum out-of-pocket costs. ASH encouraged CMS to ensure, in future rulemaking, that Part D plans do not narrow benefit coverage for a full range of drugs, including those specialized drugs required by patients with hematologic and other complex disorders.
Hemophagocytic lymphohistiocytosis (HLH), a systemic inflammatory disorder familiar to hematologists, was originally defined in many patients as an idiopathic syndrome. It is now recognized as a primary immune regulatory disorder with diverse manifestations. The syndrome involves excessive activation of T cells (most likely CD8+ T cells) that recruit and activate other immune effector cells, such as macrophages, natural killer (NK) cells, and monocytes. A retrospective report describing treatment with alemtuzumab in 22 patients with relactory HLH indicated that approximately two-thirds of patients experienced an overall partial response and 77 percent of patients survived.1,2 Two individual case reports of patients with syndromic or secondary HLH treated with ruxolitinib have been published recently.3,4 Both patients displayed decreases of inflammatory markers, though one did not experience recovery of cytopenias and died. The potential myelosuppressive effects of ruxolitinib merit continued attention in future clinical studies in this disease. A phase I trial evaluating ruxolitinib for patients with HLH is now recruiting (NCT02400463).

Targeting CD52. Alemtuzumab is a humanized monoclonal antibody directed against CD52, which depletes T cells, B cells, and monocytes. A retrospective report describing treatment with alemtuzumab in 22 patients with relactory HLH indicated that approximately two-thirds of patients experienced an overall partial response and 77 percent of patients survived to undergo HSCT.5 Use of alemtuzumab is associated with profound and long-lasting immune suppression, though in this report, the risk seemed justified by the observed benefit. Alemtuzumab is currently being evaluated in a clinical trial of patients with primary HLH (NCT04727054). A second trial is examining alemtuzumab in combination with storytold monoclonal antibody directed against IFN-γ.6

Emergence of Targeted Therapy for Hemophagocytic Lymphohistiocytosis

The development thus far of targeted therapies for HLH has illustrated two key lessons: First, animal studies have unpdated the role of specific immune mediators in causality of disease states. It is the detailed understanding of inflammatory pathways and identification of optimal targets for intervention in these models that have allowed for development of new therapies for patients. Second, even well-studied processes or interactions may have unexpected effects in pathologic contexts. Initial understanding of the perforin pathway suggested only a role in host defense, rather than the dominant role it plays in immune regulation in humans. Furthermore, before HLH was modeled in experimental models, it would have predicted the unusual immunopathologies that IFN-γ can produce. Current translational efforts are just beginning to uncover complexities of human HLH that animal models may have not revealed. There is much to learn and perhaps even more surprises to be had as therapy for HLH begins to focus on rationally derived targets.

Dr. Jordan serves on a scientific advisory committee for Novimmune.

CONVENTIONAL TREATMENT OF HLH

Conventional i.e., for patients with HLH consists of chemotherapy and immunotherapy (etoposide, corticosteroids, cyclosporin A, and sometimes intrathecal methotrexate). These regimens are typically used as a bridge to hematopoietic stem cell transplantation (HSCT). Recently reported results in a group of 369 patients treated according to the HLH-2004 study indicated that at 5.2 years of follow up, 62 percent remained alive.7 Moreover, the chemotherapy agents used in this approach have shown significant toxicities. The limitations of conventional regimes for the treatment of HLH, along with increased understanding of key inflammatory molecules, have placed greater attention on more targeted therapies for patients with this disease.

INFLAMMATORY PATHWAYS IN HLH

Animal models of HLH have demonstrated that it is a disease of acute T cell activation and recruitment of innate immune cells such as macrophages. Indeed, elimination of CD8+ T cells was demonstrated to be sufficient in preventing HLH development in mouse models of rheumatologic HLH also known as macrophage activation syndrome (MAS).8,9,10 Evidence also suggests a contribution of other inflammatory mediators in some experimental or clinical situations. High IL-6 levels have been demonstrated to have a poor prognostic significance in HLH, and IL-6 blockade has been used to successfully treat cytokine release syndrome (a close relative of HLH) after immunotherapy for cancer.11,12 IL-18 is elevated in some patients with HLH, particularly those with genetic mutations affecting the inflammasome, and blockade is therapeutic in experimental models.13,14 Furthermore, IL-1 blockade has been reported to be therapeutic in patients with MAS.15

TARGETED THERAPY FOR HLH

Several approaches to targeted therapy for HLH are currently in clinical testing, and further studies are likely (Figure).

Targeting IFN-γ. Emapalumab is a monoclonal antibody directed against IFN-γ that is being developed specifically for the treatment of HLH. An international phase II trial clinical trial is currently ongoing (NCT01818492), though an interim analysis of results was reported at the 2015 ASH Annual Meeting.16 In this study, emapalumab was initially administered at a dose of 1 mg/kg, along with dexamethasone. Of 16 patients enrolled (median age, 1.2 years), 14 received emapalumab as second-line treatment after failure or intolerance of conventional therapy. Of the 13 patients who were evaluable and who completed treatment, nine achieved a satisfactory response: Seven proceeded to HSCT, and two were awaiting transplantation with good control of HLH. Four patients had an insufficient response, two of whom died of HLH, and two were able to proceed to HSCT. IFN-γ neutralization was demonstrated in most patients by a sharp decrease in serum CXCL9. Overall, emapalumab was well tolerated with no significant safety concerns identified. This study continues to accrue patients, and development of emapalumab also continues, with open studies examining its effectiveness in secondary HLH associated with juvenile idiopathic arthritis (NCT03118154) and an observational study gathering data about IFN-γ in patients with malignancy-associated HLH (NCT02052920).

Targeting Janus kinase (JAK). IFN-γ signaling proceeds via the JAK/STAT pathway, making JAK inhibition an obvious therapeutic target. Ruxolitinib, a U.S. Food and Drug Administration–approved inhibitor of JAK1 and JAK2 can block signaling downstream of IFN-γ, IL-6, IL-10, and other cytokines. In preclinical murine models, treatment with ruxolitinib has been reported to be therapeutic, improving inflammatory pathways such as weight loss, organomegaly, cytopenias, and tissue infiltration, as well as improving survival.17,18 Two individual case reports of patients with syndromic or secondary HLH treated with ruxolitinib have been published recently.19,20 Both patients displayed decreases of inflammatory markers, though one did not experience recovery of cytopenias and died. The potential myelosuppressive effects of ruxolitinib merit continued attention in future clinical studies in this disease. A phase I trial evaluating ruxolitinib for patients with HLH is now recruiting (NCT02400463).

Targeting IL-6. IL-6 is an inflammatory cytokine that is typically elevated in patients with active disease. Interestingly, the IL-6 receptor monochlonal antibody, bevacizumab, is currently being investigated in clinical trials of patients with HLH (or MAS) associated with juvenile idiopathic arthritis. A clinical trial is currently enrolling these patients (NCT02985118).

Lessons Learned and Future Prospects

The development thus far of targeted therapies for HLH has illustrated two key lessons: First, animal studies have unpdated the role of specific immune mediators in causality of disease states. It is the detailed understanding of inflammatory pathways and identification of optimal targets for intervention in these models that have allowed for development of new therapies for patients. Second, even well-studied processes or interactions may have unexpected effects in pathologic contexts. Initial understanding of the perforin pathway suggested only a role in host defense, rather than the dominant role it plays in immune regulation in humans. Furthermore, before HLH was modeled in experimental models, it would have predicted the unusual immunopathologies that IFN-γ can produce. Current translational efforts are just beginning to uncover complexities of human HLH that animal models may have not revealed. There is much to learn and perhaps even more surprises to be had as therapy for HLH begins to focus on rationally derived targets.

Dr. Jordan serves on a scientific advisory committee for Novimmune.


When Does Monoclonal Gammopathy Acquire Significance?


Monoclonal gammopathy of undetermined significance (MGUS) is a precursor condition of multiple myeloma (MM) and lymphoid malignancies such as Waldenström macroglobulinemia (WM). It is defined by the presence of serum monoclonal protein (M protein) of 3.0 g/dL or less, in the presence of 10 percent or fewer monoclonal plasma cells in the bone marrow of asymptomatic patients. Individuals with IgG or IgA MGUS progress to MM, while those with IgM MGUS progress to WM or non-Hodgkin lymphoma. It is clear that our understanding of MGUS has improved tremendously throughout the years, but were it not for Dr. Robert Kyle, we would not know as much today.

Recently, Dr. Kyle published a seminal study on the long-term follow-up to date of 1,384 patients with MGUS—a lifelong effort he initiated more than 50 years ago to identify risk factors of progression in MGUS. In fact, it was he who coined the term “MGUS.” He advocated in support of this term over earlier nomenclature including “benign monoclonal gammopathy” and Jan Wattez-Pirenne’s 1978 description of “essential hypergammaglobulinaemia.” Dr. Kyle’s rationale behind “undetermined significance” was based on the observation that this precursor condition could either remain unchanged or evolve into MM or WM.

Dr. Kyle has since spearheaded efforts to study the long-term outcome of patients with MGUS. He initiated a large study evaluating patients with MGUS who resided in the 11 counties of southeastern Minnesota from 1960 through 1984. By way of this pioneering work, not only did he shape our understanding of MM and other hematologic malignancies, but he also laid the groundwork for future efforts in understanding cancer evolution from precursor conditions in general.

In 2002, Dr. Kyle and colleagues reported the first long-term follow-up study of this cohort, whereby the overall risk of progression of MGUS to MM, WM, amyloidosis, or lymphoma was approximately 1 percent per year. Naturally, that statistic has been extensively quoted in clinical practice ever since. A second report was published in 2003 showing a correlation between baseline M protein level in IgM MGUS patients and disease progression to lymphoma or WM. In 2005, the very same group showed that serum-free light chain (FLC) ratio had a clinically significant impact on MGUS disease progression.

In 2006, Dr. Kyle and colleagues reported the prevalence of MGUS based on a population-based cohort study among all living residents of Olmsted County, MN, as of January 1, 1995. They found that MGUS was present in 3.2 and 5.3 percent of individuals aged 50 and 70 years or older, respectively, while it was 1.5 times more common in men than women. In 2010, in another study from that cohort, the authors introduced a new clinical entity, light-chain MGUS, defined by the presence of an abnormal free light-chain ratio and increased concentration of the involved light chain, in the absence of heavy-chain expression. Its prevalence was 0.8 percent in individuals aged 50 years and older.

Now, with their recent article in The New England Journal of Medicine, published in January 2018, Dr. Kyle and his coauthors report the updated long-term follow-up data of the MGUS cohort, comprising patients diagnosed between 1960 and 1994, with a whopping median follow-up of 34.1 years. In this study, for the first time, they report shorter overall survival for MGUS patients compared to a matched control population. Furthermore, they report a higher risk of progression for IgM MGUS patients compared with non-IgM MGUS individuals. More specifically, in patients with IgM MGUS, the presence of two adverse risk factors (abnormal FLC ratio and M protein ≥1.5 g/dL) is associated with a 95 percent risk of progression at 20 years, compared with 41 percent in patients who had one risk factor and 19 percent in patients who had none. Meanwhile, in patients with non-IgM MGUS the risk of progression at 20 years is 30 percent among those who had two risk factors, 20 percent among those who had one, and 7 percent among patients who had none.

At almost 90 years of age, Dr. Kyle has uniquely characterized the progression risk of MGUS—the very entity he helped define more than 50 years ago. His monumental studies have transformed the landscape of precursor conditions in plasma cell malignancies and cancer in general. So perhaps, as suggested by many of his colleagues in the field, MGUS should be called “Kyle gammopathy” in recognition of the colossal contributions of the man who described it.

Complexity of DNA Repair From Alcohol Damage Revealed


Hematologists have long known of alcohol’s negative effects on blood cells and hematopoiesis—effects that were thought to be reversible. However, is the latter strictly true? While alcohol is not typically listed as an environmental agent causing hematologic malignancies, it is metabolized to acetaldehyde, a carcinogen that damages DNA, and chronic alcohol use is certainly associated with solid tumors, including breast, liver, colon, and esophageal. Indeed, an insidious action of alcohol on the bone marrow was revealed when Japanese patients with Fanconi anemia (FA) and elevated acetaldehyde from alcohol dehydrogenase deficiency were found to have accelerated progression to bone marrow failure. However, the interplay between alcohol, acetaldehyde, DNA damage, and its subsequent repair in hematopoietic stem cells (HSCs) has not been well understood until now.

In a recent Nature article, Dr. Juan I. Garaycoechea and colleagues found that acetaldehyde damages the DNA of mouse bone marrow HSCs, and its correction requires multiple different mechanisms of DNA repair. A wealth of prior research has taught us that the FA repair pathway protects against cumulative DNA cross-link damage. By studying patients with this rare disease and through experiments on the different FA genes, we know that this pathway is complex and involves very different DNA repair mechanisms including homologous recombination, nucleotide excision repair, and transliteration synthesis. The authors previously looked at mice with a strong FA phenotype. The mice lack Fancl2, an important FA protein involved in the recruitment of downstream DNA repair. When these mice were also deficient in aldolase dehydrogenase 2 (Aldh2-/-Fancd2-/-), the HSCs were more susceptible to acetaldehyde.

Now, in an elegant series of sequential genetic deletion experiments, the authors have defined which of the DNA repair mechanisms are needed to protect from acetaldehyde-induced DNA damage. First, they showed that Aldh2-/-Fancd2-/- mouse bone marrow had chromosomes with increased reciprocal transfer of genetic material between sister chromatids. This phenomenon, known as sister chromatid exchange, is often used as a surrogate marker for homologous recombination events. The number of sister chromatid exchanges was potentiated on exposure to alcohol and indicated that acetaldehyde induces homologous recombination DNA repair. They then confirmed this by showing that DT40 cells lacking both homologous recombination and FA genes were more sensitive to acetaldehyde than cells deficient in only one.

Next, they used micronuclei in enucleated erythrocytes and multiple FISH markers to examine DNA damage. In Aldh2-/-Fancd2-/- mice, there is a basal increase in DNA damage, and this was exacerbated fourfold by exposure to ethanol. This shows that in the presence of normally functioning homologous recombination repair machinery, the FA pathway is also required to repair chromosome breakage from acetaldehyde. They then looked at mice lacking the FA repair gene Fanca and the non-homologous end-joining repair (NHEJ) protein KU70. These mice were anemic, had fewer HSCs, had more DNA damage, and were more sensitive to acetaldehyde. This suggested that NHEJ repair is also important for repair of acetaldehyde-induced DNA damage, at least in the absence of the FA pathway.

Finally, serial transplantation experiments with either one or five HSCs showed that Aldh2-/-Fancd2-/- mice have HSCs that are less able to engrant and contribute to hematopoiesis in recipient mice. By sequencing the recipient mouse bone marrows, they showed that acetaldehyde causes specific structural DNA damage involving insertions, deletions, translocations, and rearrangements. Aldh2-/-Fancd2-/- mice also had hematopoietic and progenitor stem cells with increased expression of p53 and the poor bone marrow engraftment improved on a p53 null background.

In summary, Dr. Garaycoechea and colleagues have provided us with further insight into the types of DNA damage wrought by alcohol and the different mechanisms required to repair them. If unrepaird, alcohol-induced DNA damage has long-term deleterious effects on the function of mouse hematopoiesis, particularly when abnormalities in DNA repair are present. This explains the clinical findings in patients with FA carrying negative variants of ALCDO2. It also has broader implications for understanding the toxic effects of alcohol in both nonhematopoietic cells and HSCs, and for the 540 million people worldwide who are deficient in aldolase dehydrogenase.


EDWARD CHEW, MBBS, AND ANDREW ROBERTS, MBBS, PHD
Dr. Chew and Dr. Roberts indicated no relevant conflicts of interest.
RNA Methyltransferases As a New Therapeutic Target in Leukemia


Many of the recent exciting advances in the therapy and understanding of myeloid leukemia pathogenesis have centered on the process of DNA methylation. This includes the discovery of mutations in enzymes that demethylate DNA (such as mutations in DNMT3A) and the machinery involved in DNA demethylation (including TET2 and IDH1/2 mutations). Additionally, several therapies commonly used in myeloid leukemias impact the process of DNA methylation such as DNA methyltransferase inhibitors (decitabine and 5-azacitidine), as well as mutant IDH1/2 inhibitors.

While these advances have focused on the idea that DNA residues can undergo reversible methylation, it has been known for some time that RNA residues can also be modified in a reversible manner (reviewed recently). In fact, more than 100 different RNA modifications have been discovered, but the functional significance of modifications on RNA is largely not well understood. Now, two studies have highlighted that the enzyme METTL3, which places a methylation mark on RNA known as N6-methyladenosine (or m6A), may be a novel dependency in acute myeloid leukemia (AML). The m6A modification is placed on coding as well as noncoding RNAs and has been shown to play a role in regulating mRNA translation to produce protein. Although they used distinct approaches, both studies found that METTL3 is required for the survival of AML cells, but not normal human or mouse hematopoietic progenitors, and that METTL3 is unique in that the mRNA and protein level in AML is conserved in normal cells. In fact, in both reports, overexpression of wild-type METTL3, but not an enzymatic dead version, enhanced the growth of AML cells.

Given the results shown here, one key question is how an enzyme that modifies RNA would be required for AML cell survival and promote leukemogenesis. To address this question, Dr. Ly P. Vu and colleagues mapped the location of m6A in the RNA of AML cells at single-nucleotide resolution. Because the m6A modification on RNA has been previously shown to affect the translation of mRNAs by the ribosome, the authors also determined the mRNAs that were occupied by the ribosome in the presence and absence of m6A. This effort revealed that m6A-containing transcripts regulated by METTL3 conspiciously included c-MYC, BCL2, and PDK1 – three factors that are well known to be proto-oncogenic. METTL3 knockdown influenced the translation of mRNAs encoding these transcripts and, consequently, regulated protein levels of MYC, BCL2, and PTEN.

Similar to the results by Dr. Vu and colleagues, Dr. Isaba Barbieri and team identified that METTL3 is also required for AML cell survival using a CRISPR/Cas9 screen focusing on a large number of genes encoding known or putative RNA-modifying enzymes. This revealed that Mettl3, Mettl4, Mettl1, and Mettl6 are all required in AML cells. Generation of Mettl3 and Mettl4 form a complex (with METTL3 encoding the enzymatic component of the complex), they decided to focus on METTL3/METTL4 for further studies. Nonetheless, the results from their CRISPR screen suggest that numerous additional RNA-modifying enzymes may be distinctly required in AML over normal cells.

One key question related to the study of RNA m6A catalysis is how the METTL3/METTL4 enzymatic complex is recruited to its RNA substrates. Dr. Barbieri and coauthors therefore tested whether METTL3 might regulate RNA methylation of transcripts by binding to chromatin encoding these RNAs. They thus performed immunoprecipitation using a CHiP-seq (chromatin immunoprecipitation followed by next-generation sequencing) and found that 1) METTL3 binds chromatin, largely at transcription start sites, and 2) transcripts derived from METTL3-bound promoters harbor m6A within their coding sequence. These data suggest that METTL3 regulates mRNAs derived from their chromatin target genes.

Overall, these two studies identify an enzyme that appears to be overexpressed in AML and on which AML cells can become dependent. While the molecular basis for this unique requirement of METTL3 in AML over normal cells is not yet clear, these studies provide a strong rationale for the development of pharmacologic approaches to block m6A placement as a novel therapy for AML. It will also be interesting to study whether METTL3 plays a role in normal hematopoiesis at any point and if it is distinctly required in other myeloid malignancies such as myelodysplastic syndromes or myeloproliferative neoplasms. Finally, the “eraser” of the m6A mark (an enzyme known as ALKBH5) is an α-ketoglutarate dependent enzyme, the activity of which may be influenced by IDH1/2 mutations. Further studies to clarify the role of ALKBH5 in cancer pathogenesis will therefore be important as well.


Can Iron Every (Other) Day Keep the Doctor Away?


Iron deficiency, with or without anemia, is extremely widespread, representing a major public health problem. In the United States, the prevalence of iron deficiencies (defined by the log ratio of transferrin receptor to ferritin) in women ages 12 to 19 years and 20 to 49 years is approximately 9 percent for both age groups according to National Health and Nutrition Examination Study data (2003-2006). Its treatment includes addressing the underlying cause and replacing the iron deficit. However, exactly who benefits from correction and how best to administer iron remain open questions. In clinical practice, oral iron supplementation at various doses and dosing intervals is the most common replacement route, complicated by poor absorption and gastrointestinal adverse effects that contribute to nonadherence in up to 50 percent of patients. Consequently, oral iron supplementation at various doses and dosing intervals is the most common replacement route, complicated by poor absorption and gastrointestinal adverse effects that contribute to nonadherence in up to 50 percent of patients.

Hepcidin (Hamp) is the key regulator of mammalian systemic iron balance. It acts on the iron export protein ferroportin causing its internalization and degradation. High hepcidin levels inhibit intestinal dietary iron absorption and macrophage red blood cell (RBC) iron recycling. A high iron supplementation acutely increases circulating plasma hepcidin levels. This physiology was elegantly tested in a short-term clinical study: Women with depleted iron stores and without anemia (ferritin ≤ 20 ng/mL) received various doses and frequencies of oral iron administered for two to three days. Higher or more frequent doses of iron raised circulating hepcidin levels and reduced subsequent fractional iron absorption.

To address whether this effect on hepcidin levels and iron absorption occurs and persists during long-term supplementation, Dr. Nicole Stoffel and colleagues conducted two open-label randomized controlled trials assessing iron absorption in iron-depleted women (ferritin ≤ 25 μg/L; ages 18 to 40 years). Within-individual comparisons were performed. The primary outcomes of both studies were iron bioavailability (total and fractional iron absorption, measured by radioisotopic iron incorporation into RBCs) and serum hepcidin levels. In the first study, 40 women were randomly assigned to either 60 mg of oral iron (as FeSO4) administered each morning for 14 days, or the same dose on alternate days for 28 days. At the end of treatment (14 or 28 days, for the consecutive- and alternate-day groups, respectively), geometric mean cumulative fractional iron absorptions were 16.3 percent in the consecutive-day group versus 21.8 percent in the alternate-day group (p=0.0013), and cumulative total iron absorption was 131.0 mg in the consecutive-day group versus 175.3 mg in the alternate-day group (p=0.0010). During the first 14 days of supplementation in both groups, serum hepcidin level was higher in the consecutive-day group than the alternate-day group (p=0.001). There was a trend toward decreased nausea in the every-other-day group.

In the second study, women were assigned to two groups stratified by comparable serum ferritin levels. One group received 120 mg of oral iron each morning (n=10), and the other received 60 mg orally in the morning and 60 mg orally in the evening (n=10), for three consecutive days. Fourteen days after the final dose, the groups each crossed over to the other regimen. No significant differences were seen in fractional or total iron absorption between the two dosing schemes. Twice-daily divided doses resulted in a higher serum hepcidin concentration than once-daily dosing (p=0.013).

Nicely informed by basic iron physiology, this study suggests that alternate-day, rather than twice-daily, dosing of oral iron can overcome the hepcidin-mediated block of iron absorption. While not addressed in this study, patient tolerability to and compliance with oral iron might improve with this approach. Additional studies are needed to determine whether this observation holds in iron-deficient patients with anemia and in other clinical settings. If it does, this simple strategy could transform the therapy for this common medical condition.

**Novel Insights From Comprehensive Genomic Profiling of T Cell Acute Lymphoblastic Leukemia**


T cell acute lymphoblastic leukemia (T-ALL) is a malignancy of lymphoid origin that accounts for 15 to 25 percent of ALL cases. Survival for patients with both B-ALL and T-ALL has improved substantially throughout the past 30 years, as more than 80 percent of children diagnosed with ALL are cured with modern therapy. Unfortunately, not all patients with T-ALL are cured, and the prognosis for patients with relapsed T-ALL is dismal. More robust genomic characterization of T-ALL blasts has the potential to improve understanding of T-ALL biology, identify novel therapeutic targets, and improve risk stratification. Identifying patients at diagnosis who are likely to relapse could lead to potential modifications in therapy that include intensification of conventional cytotoxic chemotherapy or integration of novel therapies.

In 2017, Dr. Yu Liu and colleagues published the largest comprehensive genomic analysis of children and young adults with T-ALL. They performed RNA sequencing, copy number analysis, and whole-exome sequencing on 264 children and young adults with T-ALL who had consecutively enrolled on the Children’s Oncology Group AALL0434 clinical trial (NCT00408005) if both tumor and remission samples were available. They identified 106 putative driver genes, approximately 50 percent of which had not been previously described. They integrated DNA copy number alteration data, sequence mutation, and structural variant/rearrangement, and they identified 10 potentially targetable functional pathways that were recurrently mutated. These included, in order of frequency from most to least common, transcriptional regulation, cell cycle regulation and tumor suppression, Notch1 signaling, epigenetic regulation, PI3K/Akt/mTOR signaling, Jak-Stat signaling, MAPK (RAS) signaling, ribosomal function, ubiquitination, and RNA processing (Figure). They found a strong correlation between the type and frequency of genetic alterations, the developmental stage of TALL blasts, and different T-ALL subgroups. For example, alternations in PI3K/Akt/mTOR signaling were prevalent in the TAL1 subgroup, whereas alterations in Jak-Stat and MAPK signaling were prevalent in the LMO2/LYL1 and HOX3A subgroups. Finally, they established that multiclonal and subclonal mutations were common.

While the authors made many seminal observations with this groundbreaking study, there were a few limitations to the analysis. First, only a small percentage of samples included whole-genome sequencing. Numerous recent studies have demonstrated the importance of genomic alterations in noncoding regions in T-ALL pathogenesis. Second, only 75 percent of the patients included in the cohort relapsed. Thus, the study was not powered to correlate genetic lesions with outcome. A cornerstone to the improvement in ALL survival has been patient risk stratification based on sentinel genetic alterations and measurement of minimal residual disease (MRD). While MRD is successful in identifying most TALL patients who have a worse outcome, most relapses occur in patients classified as lower risk by MRD. Comprehensive genomic analysis of a larger population of relapsed patients has the potential to identify genetic alterations or groups of alterations that may predict outcome. Lastly, one of the criteria for inclusion in the analysis was availability of a remission sample for germline DNA. This excluded some patients who were chimeric (i.e., had induction failures).

In summary, Dr. Liu and colleagues performed a robust, comprehensive genomic analysis of patients with T-ALL. They made many important observations that are directly translatable and will improve understanding of T-ALL biology. Hopefully, these observations will lead to the development of new therapies that may improve survival for children and young adults with T-ALL.

---

2. Mansur MR, Abraham BJ, Andrei L, et al. Oncogene regulation: An oncogenic super-enhancer formed through somatic mutation of a noncoding children and young adults with T-ALL. Hopefully, these observations will lead to the development of new therapies that may improve survival for patients with relapsed T-ALL. Second, only 7.5 percent of the patients included in the cohort relapsed. Thus, the study was not powered to correlate genetic lesions with outcome. A cornerstone to the improvement in ALL survival has been patient risk stratification based on sentinel genetic alterations and measurement of minimal residual disease (MRD). While MRD is successful in identifying most TALL patients who have a worse outcome, most relapses occur in patients classified as lower risk by MRD. Comprehensive genomic analysis of a larger population of relapsed patients has the potential to identify genetic alterations or groups of alterations that may predict outcome. Lastly, one of the criteria for inclusion in the analysis was availability of a remission sample for germline DNA. This excluded some patients who were chimeric (i.e., had induction failures).

---

Beyond Ibrutinib for Mantle Cell Lymphoma


Despite advances in the treatment of mantle cell lymphoma (MCL) in the past few decades, and the development of new agents with activity in this disease, it remains an incurable malignancy with a relatively short survival compared with other treatable but incurable B cell non-Hodgkin lymphomas (B-NHL). With cure remaining elusive, the discovery of well-tolerated and effective therapies is an important goal in the management of patients.

The Bruton’s tyrosine kinase (BTK) inhibitor ibrutinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of relapsed MCL in 2013, based on a response rate of 68 percent and a duration of response of 175 months in a phase II study.1 Only about one-fifth of patients, however, had a complete response, bleeding complications and atrial fibrillation were present in 5 to 10 percent of patients, and infections occurred in up to one-third of patients, including invasive central nervous system aspergillus infections. These toxicities are thought to be due to the fact that ibrutinib is a relatively promiscuous tyrosine kinase inhibitor that also inhibits both Tec and IL-2–inducible T cell kinase.

Acalabrutinib, however, is a more specific BTK inhibitor and therefore may have a more favorable adverse effect and toxicity profile. Additionally, it is dosed twice daily, which investigators postulate may result in improved BTK inactivation given that, like ibrutinib, it is a covalent inhibitor, and BTK synthesis in the malignant lymphocyte may be faster in ibrutinib inactivation than with acalabrutinib. This study was not powered to correlate genetic lesions with outcome. A cornerstone to the improvement in ALL survival has been patient risk stratification based on sentinel genetic alterations and measurement of minimal residual disease (MRD). While MRD is successful in identifying most TALL patients who have a worse outcome, most relapses occur in patients classified as lower risk by MRD. Comprehensive genomic analysis of a larger population of relapsed patients has the potential to identify genetic alterations or groups of alterations that may predict outcome. Lastly, one of the criteria for inclusion in the analysis was availability of a remission sample for germline DNA. This excluded some patients who were chimeric (i.e., had induction failures).

In summary, Dr. Liu and colleagues performed a robust, comprehensive genomic analysis of patients with T-ALL. They made many important observations that are directly translatable and will improve understanding of T-ALL biology. Hopefully, these observations will lead to the development of new therapies that may improve survival for children and young adults with T-ALL.
Physicians Beware: Direct Oral Anticoagulants Do Interact With Some Commonly Used Drugs

Direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban) are increasingly prescribed for prevention of stroke in the setting of atrial fibrillation. These agents, however, do not require laboratory coagulation monitoring (i.e., international normalized ratio [INR]); have fewer dietary restrictions, and are associated with a lower risk of intracranial bleeding in patients with atrial fibrillation. An additional important advantage is the limited number of drugs that interact with DOACs compared with the extensive list of interactions with warfarin. However, there are some important DOAC-drug interactions that can lead to serious consequences for patients.

Dr. Shang-Hung Chang and colleagues conducted a retrospective cohort study of a Taiwan national health insurance database to examine the association between concomitant prescription of DOACs with other selected agents and the risk of major bleeding. They focused on agents that share the same metabolic pathways as DOACs, in particular CYP3A4 (fluconazole, ketoconazole, itraconazole, danazol, ergot alkaloids, and chemicals that transport system P (P-glycoprotein); digoxin, verapamil, dilatiazem, amiodarone, or cyclosporine); or both mechanisms (atorvastatin, erythromycin or clarithromycin, dideoxiribonuclease, rifampin, or phenytoin).

Major bleeding was defined as bleeding that required hospitalization or an emergency department visit with a presence of intracranial bleeding or gastrointestinal, urogenital, or other bleeding. Comorbidities were included in the model as covariates (e.g., components of Charlson comorbidity index, CHADS2-VASC scores), and a propensity score was used to adjust for confounding by indication for medications ordered for the same condition.

A total of 81,930 patients with nonvalvular atrial fibrillation who received a DOAC were identified (rivaroxaban, 59.1%; dabigatran, 49.7%; apixaban, 14.1%; edoxaban not available). The mean age of the cohort was 74.7 years, 55 percent were men, and baseline average CHADS2-VASC score was 3.9. The DOAC-selected drug combinations associated with an increased risk of major bleeding are summarized in the Table.

Of special interest to hematologists, neither cyclosporine (P-gp inhibitor) nor the other azole antifungal agents (strong CYP3A4 inhibitors) were associated with an increased risk of bleeding in the Taiwan cohort. However, the number of prescriptions for those agents was limited, and other studies suggest the interaction could be significant.

Although this cohort provides some real-world data on the potential for interaction between DOACs and selected drugs, the results should be interpreted with caution. Important risk factors for bleeding, such as creatinine clearance and liver function, could contribute to the increase in this study. Consensus scores can only adjust for known variables. As a general rule, until further data are available, hematologists should use caution when prescribing anticoagulants, antifungal agents, cyclosporine, and certain antibiotics (i.e., rifampin, erythromycin, or clarithromycin) for patients taking a DOAC. On the flip side, patients who require clopidogrel for patients taking a DOAC. On the flip side, patients who require antiplatelet therapy can guide others along this path.

Deconstructing the Threat of the Fava Bean

Pythagoras, who I believe was also somewhat accomplished in mathematics, was the first person to record that the ingestion of fava beans could be dangerous. However, his claim is qualified with magnificent equiscope in this sublime review by Drs. Lucio Luzzatto and Paolo Arrese. "This gives him a place in nutrition science but not in nutrigenomics: it seems he did not realize that the danger depended on the genotype of the person eating the beans."

Living, as we are, in a time in which the exact date of online publications is often scrutinized, Pythagoras could at least console himself with the knowledge that he was 2,500 years ahead of his peers.

It is now 62 years since glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency was discovered in people who experienced hemolytic crises following ingestion of the antimarial primquine in 1956. This review, which focuses on one of the three syndromes of G6PD deficiency (the others being neonatal jaundice and drug-induced hemolytic anemia) reveals how favisim continues to hold a place as an exemplar of personalized medicine.

As the authors state, "In favisim, there are two main actors: the bean and the red cell. Fava beans and genetic susceptibility must come together to elicit the outcome of favisim. Ironically, the fava bean plant (Vicia faba; known to many as the broad bean) may have been the first plant to be domestically cultivated and produces a protein-rich bean that can be eaten hot or cold. The problem is that the bean’s protein content can include as much as 2 percent vicine and convicine, which are converted in the gut to divicine and isouramil. These highly redox proteins are likely to complex with the iron of the bean, but produce reactive oxygen species (ROS) including the superoxide anion and hydrogen peroxide, which rapidly oxidize NADPH and glutathione. These molecules are normally detoxified by catalase and glutathione peroxidase, in enzymatic reactions that depend on NADPH. Because NADPH levels are very low in G6PD-deficient red cells, these undergo severe oxidative damage. A characteristic feature of favisim is that intracellular and extracellular hemolysis coexist. The intracellular damage is easy to explain, whereas extracellular hemolysis occurs only as complement is activated by the cell antigens and p-hydroxy acidosis.

More than 200 different genetic mutations are known to cause G6PD deficiency and most of them probably can elicit favisim. The gene is present on the X chromosome, so boys are more commonly affected than girls, though random X inactivation in heterozygous females can also lead to their susceptibility. The complete loss of G6PD function is lethal, so all mutations retain varying degrees of enzymatic activity. G6PD mutations are one of the myriad genetic legacies of the tectonic forces of evolutionary selection mediated by malarial infection on the human genome. Heterozygous levels of G6PD offer relative protection against parasite carriage but this benefit to the population has come at the expense of considerable morbidity and mortality for millions of people. Indeed, favisim remains probably the most common cause of acute hemolytic anemia.

Robert Heinz described the supravalvular stain to detect his “bodies” in blood smears back in 1890, but it remains a valuable test to visualize oxidized hemoglobin fragments. “This test takes time and must be performed by a competent hematologic technologist,” according to Drs. Luzzatto and Arrese, “but it does not require expensive equipment or reagents; the test is unlikely to be performed nowadays.” Additional tests of importance are an acridine orange blood count and a blood film, which will demonstrate the remnants of the battlefield of oxidative damage on red cells. Other possible features include “hemoglobins” and “blister cells,” as well as the spherocytes and dense red cells that are at an earlier stage of damage. The urine is dark and full of hemoglobin, and the level of unconjugated bilirubin in the serum is very high. “The parents, if asked, almost always report that their son has dark urine and has eaten fava beans.”

A well-described case history brings a topic alive as the authors describe the typical scenario of a boy aged two to 10 years, with acute fatigue, pallor, and abdominal pain. Intracutaneous hemolysis is apparent from the dark urine and abdominal symptoms resulting, as in paroxysmal nocturnal hemoglobinuria, from the consumption of nitric oxide from free hemoglobin. Jaundice and splenomegaly are features of the extracellular contribution of red cell destruction.

“Once a diagnosis of favisim has been made, management is usually not difficult”, the authors assure. “The first concern is that chemotherapy is contraindicated, but the treatment, for once, is straightforward. Mild cases may need only hydration and symptomatic treatment, but for others, blood transfusion is required and is rapidly effective. Transfusion should be given where hemoglobin concentration is lower than 70 g/L and at a higher threshold if there is binkus hemolysis.”

Red cell biology has led in many areas of medical science, and this is not a review that rests in the past. The future looks toward elimination of the burden of favisim. One approach is through neonatal screening and appropriate risk management. A population-based solution would be to introduce natural or genetically engineered plants which are selected for low production of vicine. “At a time when most countries declare that preventive medicine is a priority, the seeds from the Fava bean must be potent eradication of this disorder. In an era dominated by “personalized medicine,” these reflections remind us of how long this has been at the center of hematology practice and how we can guide others along this path.

Concurrent Drug Adjusted Rate Difference* Adjusted Incidence Rate Difference per 1,000 Person-years#
Fluconazole 2.35 (95% CI, 1.80-3.07) 138 (99% CI, 81-196)
Phenytoin* 1.94 (95% CI, 1.59-2.36) 52 (99% CI, 32-72)
Rifampin 1.57 (95% CI, 1.02-2.41) 37 (99% CI, 2-72)
Amiodarone* 1.37 (95% CI, 1.25-1.50) 14 (99% CI, 10-18)

*Reference was DOAC alone.
#Not significant for apixaban, but smaller proportion of users.

LORI-ANN LINKINS, MD, MSC (CLIN EPI), FRCP Dr. Linkins indicated no relevant conflicts of interest.
PAUL MOSS, MD Dr. Moss indicated no relevant conflicts of interest.
Surround and Protect! Expression of PD-L1 on Tumor-Associated Macrophages in Classic Hodgkin Lymphoma


Classic Hodgkin lymphoma (cHL) is a lymphoma of B cells where the large neoplastic cells – Hodgkin Reed-Sternberg (HRS) cells – are typically rare and often surrounded by a rich inflammatory background. Yet, despite the exuberant inflammation, the lymphoma growth evades host-versus-lymphoma immune surveillance and, without therapy, is rapidly fatal. Gene expression profiling of the inflammatory cells singled out tumor-associated macrophages (TAMs) as correlating with poor outcomes.1 In 2010, Dr. Christian Steidl and colleagues reported that cases of cHL with increased TAMs (marked by CD68) had significantly worse progression-free survival in both univariate and multivariate analysis as well as with 10-year disease-specific survival (p = 0.003 for all analyses), and that this variable outperformed the International Prognostic Score.2 However, with the collective level of understanding at the time, these findings were largely phenomenological, and subsequent literature in the field provided conflicting evidence. For pathologists, after an initial flurry of CD68 stains, the practice of enumerating TAMs fell out of favor. However, Dr. Claudio Agostinelli recently found that increased CD68+ TAMs have again been implicated in poor outcomes in patients with negative fluorodeoxyglucose (FDG) PET scans after two courses of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).3

Two recent papers have clarified the role of inflammation, including TAMs, in prognosis of cHL. In the first article, Dr. Peter Hollander and colleagues studied the expression of PD-1 and PD-L1 in the microenvironment of cHL and found inferior event-free survival (EFS) in patients with high levels of expression of these markers with conventional chemotherapy regimens. They found that patients with high levels of PD-1 expression on lymphocytes and monocytes (≥10% positive cells, as determined by digital image analysis of immunohistochemical stains) had shorter EFS compared with those who had low expression (p=0.002; univariate hazard ratio, 1.91; multivariate p=0.02; Figure 1A). Similarly, patients with high levels of PD-L1 (≥5% positive cells) had shorter EFS compared with those who had low expression (p=0.01; univariate hazard ratio, 1.74; multivariate p=0.03) and shorter overall survival (multivariate p<0.03; Figure 1B and 1C). Although this study limited their assessment of the tumor microenvironment to background lymphocytes and monocytes (excluding HRS cells, granulocytes, and TAMs), the authors acknowledged that the poor outcomes associated with PD-L1 expression might be in part due to PD-L1-positive macrophages.

In a second article, Dr. Christopher D. Carey and colleagues specifically identified PD-1+ lymphocytes and PD-L1+ macrophages and determined their spatial relationship to the HRS cells in an elegant study using multiplexed immunofluorescence and digital image analysis. They verified and quantitated the enrichment of PD-L1+ TAMs in proximity to HRS cells compared with PD-L1- TAMs (p<0.001; Figure 2A). Additionally, they found enrichment of CD4+PD-1+ T cells in proximity to, and directly contacting, both HRS cells (p<0.01 for increased proportion of cells in physical interaction with HRS cells and PD-L1+ TAMs) (p=0.004; Figure 2B).

The findings by Dr. Carey and colleagues create a vivid image of the relationships within the tumor microenvironment of cHL with PD-L1+ HRS cells both directly interacting with PD-1+ CD4+ T cells and recruiting their own flanking guard of PD-L1+ TAMs that further interact with PD-1+CD4+ T cells (Figure 3). Extensive PD-L1/PD-1 engagement in the immediate vicinity of HRS cells defines an “immunoprotective niche” to suppress T cell activation and effective antitumor immunity.

These results help explain the high overall response rates to PD-1 blockade strategies in relapsed/refractory cHL, with 66.3 percent objective response rates (ORR) to nivolumab and 69.0 percent ORR to pembrolizumab.4,5 In the case of nivolumab, response was correlated with PD-L1 expression in HRS cells.6 The findings of Dr. Carey and colleagues suggest that the correlation with PD-L1 expression on TAMs should be examined as well.

These studies illuminate the etiology of the previously reported association between high macrophage counts and poor response to various traditional chemotherapy regimens, as well as the remarkable responses to PD-L1-directed immunotherapy in relapsed/refractory cHL. TAMs surround the HRS cells and interact closely with CD4+-positive T cells to shield the HRS cells, effecting a Jedi mind trick on the immune system (“these are not the HRS cells you are looking for...”). These findings support an increased role of PD-1 blockade strategies in the treatment of cHL. Additionally, this study reiterates the need for pathologists to enumerate TAMs and their PD-L1 expression in cases of cHL for prognostic and immunotherapeutic purposes.
New ASH Summit Encourages Practical, Elevated Dialogue on Emerging Immunotherapies

The rise of immunotherapies for treating hematologic diseases is one of the most exciting developments in medical science in recent years. The October 2017 “Focus on Immunotherapy” special issue from *ASH Clinical News* discussed six recently approved drugs as well as nearly two dozen clinical trials that are evaluating immunotherapeutic agents (available at [www.asclincialnews.com](http://www.asclincialnews.com/special/issues)). As the field grows, these numbers are likely to swell in the next few years. On the research front, immunologic treatments of hematologic malignancies are one of the six key priorities of the ASH Agenda for Hematology Research, which specifically urges further study of the use of immune-based therapeutic strategies, improved drug efficacy and reduced toxicity, and enhancements to the effectiveness of existing therapies (learn more at [www.hematology.org/researchagenda](http://www.hematology.org/researchagenda)).

To further build on this momentum and continue leading the charge in this area, ASH has designed the ASH Summit on Emerging Immunotherapies for Hematologic Diseases — a new two-day summit that will convene researchers, clinicians, industry scientists, policy makers, and other critical stakeholders to examine the clinical and preclinical factors influencing the immunotherapeutics pipeline. Below, Program Co-Chairs Drs. Catherine Bollard, Rodrigo Calado, Sergio Giralt, and Jeffrey Miller share some personal thoughts on their hopes for the summit, as well as who should attend, and why.

What’s most exciting to you about this summit, and what aspects do you feel will engage attendees the most?

**Dr. Catherine Bollard:** In this summit, attendees will have a unique opportunity to facilitate interactions between regulators, academia, and pharma, and have exciting opportunities for discussion.

**Dr. Rodrigo Calado:** It is critical that we bring together professionals working on different aspects of immune therapies, providing an environment of complementary expertise. There will also be investigators on immune therapies for different disorders, malignant and nonmalignant, which may foster exchange of experiences and approaches.

**Dr. Sergio Giralt:** This will be the first comprehensive meeting exploring the impact of immunotherapies on the practice of hematology. Experts will be addressing areas of practical interest for both the academic and community practitioners. We will be discussing topics such as hematologic toxicities seen in cancer patients receiving immunotherapies, establishing CAR T programs and new CAR T constructs and other immunotherapies.

**Dr. Jeffrey Miller:** We have an exciting agenda with national leaders coming together to educate the hematology community on their state-of-the-art research focusing on cancer and other hematologic disorders. The main goal is to get the audience up to speed on the latest research. The venue is bidirectional and invites active participation to contribute and prioritize studies to synergize as a community.

**How do events such as this one advance hematology and immunotherapy research specifically? What makes ASH’s approach to this topic unique?**

**CB:** The focus is solely on immune-based therapies for blood disorders bringing together leaders in the field from (as highlighted above) academia and industry, which will advance the dialogue and potential for collaboration to move novel therapeutic platforms from the bench to the bedside and beyond.

**RC:** This is an opportunity to experience exchange, discussions, and the emergence of new and innovative ideas. The discussions during the meeting will help to guide research on immune therapies in the future. There will be a good balance between basic, translational, and clinical research to be presented and discussed at the summit, as well as topics to help physicians and scientists walk through the development of novel therapies. It certainly can have an impact on patient care.

**SG:** Raising awareness can result in increased funding opportunities for cooperative research; we’re also helping to create networks of investigators and physicians with similar interests. Additionally, ASH has taken a unique approach in looking at both cellular and noncellular immunotherapeutics, while many other meetings have focused on one or the other. This summit focuses on both.

**JM:** Beyond current state of the art, our goal is to provide a sounding board for next-priority studies and critical combinations, and greater understanding of how to navigate industry and regulations. We are excited that the U.S. Food and Drug Administration (FDA) has agreed to participate in this meeting. The venue is geared at senior, mid-career, and junior investigators, as well as trainees, and promises to provide an education for all by peers in the field.

**After taking part in the summit, what do you most want the attendees to walk away with?**

**CB:** Hopefully attendees will walk away with a feeling of excitement about this rapidly changing immunotherapy field and its impact. Specifically, they will have a better understanding regarding how this therapeutic platform offers incredible opportunities not only for the advancement of the science (i.e., the immunobiology of blood disorders) but also for the “real life” impact of these treatments for our patients (i.e., curing all blood diseases with immune-based therapies).

**RC:** Attendees should take advantage of the different scientific and clinical approaches to be presented and discuss them. This will help facilitate the development and expansion of novel concepts to be tested in the future.

**SG:** Immunotherapeutic treatments will be part of everybody’s practice, and awareness of indications and toxicities will be essential to providing the best care for our patients.

**JM:** Attendees need to understand changes in the hematology field given the FDA approval of two gene-modified T-cell products. Many of us believe this is the tip of the iceberg, and many more will come. The intent is to educate and prepare investigators and their institutions for what is to come. There is a clinical component to changes in standard care, as well as many opportunities to learn and get involved in research objectives for the hematology community.

*The ASH Summit on Emerging Immunotherapies for Hematologic Diseases will take place from July 12 to 13, 2018, at the Omni Shoreham Hotel in Washington, DC. For more information on the summit and to take advantage of advance registration, visit [www.hematology.org/immunotherapies](http://www.hematology.org/immunotherapies).*
**Antiphospholipid Syndrome: Can the Direct Oral Anticoagulants Be Used?**

**STUDY TITLE:** Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS)

**CLINICALTRIALS.GOV IDENTIFIER:** 02157272

**PARTICIPATING CENTERS:** Multicenter study under the leadership of University of Padova, Italy

**ACCRUAL GOAL:** 537 patients originally; however, the study terminated January 30, 2018, after 121 patients enrolled, because of “unbalance in the composite endpoint between arms.”

**STUDY DESIGN:** TRAPS is a randomized, controlled, open-label, noninferiority study investigating rivaroxaban 20 mg once daily compared to warfarin (target international normalized ratio of 2.0-3.0) in patients with definite antiphospholipid syndrome (APS) with a history of thrombosis, either arterial, venous or biopsy-proven microvascular, and triple-positive antiphospholipid antibody (APLA) tests. “Positivity” is defined by at least moderately elevated anticardiolipin and anti-β2-glycoprotein-I IgG or IgM antibodies as classified by the Sydney criteria, and a positive lupus anticoagulant. The primary outcome is a composite of acute arterial thrombosis (arterial or venous), major bleeding, and death.

**Rationale:** Warfarin is the main anticoagulant used in patients with APS who require anticoagulation, but management with warfarin can be challenging. Use of a direct oral anticoagulant (DOAC) with a predictable anticoagulant effect and not requiring monitoring would be an attractive treatment alternative. Some retrospective cohort publications have suggested that DOACs may be an acceptable and safe alternative to warfarin in the secondary prevention of thrombosis in APS,14,15,22,23 but other publications have cautioned against their use because of the risk of DOAC failure.16,17,40 Prospective, randomized data are obviously needed to determine efficacy and safety of DOACs in patients with APS.

**Comment:** The strengths of the TRAPS trial are its prospective, randomized design, relatively large size (anticipated n = 537): homogeneous patient population by laboratory parameters (all patients are triple positive for APLA), and enrollment of the higher thrombogenic APS patients (i.e., those who are triple positive). The study was prematurely terminated at the end of January 2018 when an interim analysis showed an “unbalance in the composite outcome between arms.” The potential weaknesses are: 1) the study was terminated prematurely because of “unbalance in the composite endpoint between arms.” It suggests that we will learn something clinically impactful once the data are made publicly available.

For the clinician who treats patients with APS, it is exciting to hear that the TRAPS study was prematurely terminated because of an “unbalance in the composite endpoint between arms”. It suggests that we will learn something clinically impactful once the data are made publicly available.


— Stephan Moll, MD

Dr. Moll indicated no relevant conflicts of interest.

### APS Studies Investigating the Benefit of DOACs

<table>
<thead>
<tr>
<th>Title</th>
<th>Clinicaltrials.gov ID</th>
<th>Principal Investigator (Country)</th>
<th>Patient Population</th>
<th>Treatment</th>
<th>Design</th>
<th>Outcome</th>
<th>Source(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAPS</td>
<td>02157272</td>
<td>V. Pengo (Italy)</td>
<td>H/o thrombosis (arterial or venous or microvascular) + triple APLA positive</td>
<td>Rivaroxaban 20 mg (or 15 mg for GFR 30-50 mL/min) qd versus warfarin, INR 2-3</td>
<td>Randomized, open-label</td>
<td>Recurrent thrombosis (arterial or venous)</td>
<td>537</td>
<td>121</td>
</tr>
<tr>
<td>ASTRO-APS</td>
<td>02295475</td>
<td>S.C. Wolter (USA)</td>
<td>Patients with APS (definite, likely, or historical) and VTE ≥ 6 months ago, on anticoagulation</td>
<td>Apixaban 5 mg bid versus Warfarin, INR 2-3</td>
<td>Randomized, open-label</td>
<td>Pilot + feasibility study to identify, recruit, randomize + follow patients. Secondary outcomes: recurrent thrombosis, bleeding</td>
<td>200</td>
<td>41</td>
</tr>
<tr>
<td>None</td>
<td>02926170</td>
<td>J. Cortes (Spain)</td>
<td>H/o arterial or venous thrombosis treated with acenocoumarol ≥ 6 months ago, on anticoagulation</td>
<td>Rivaroxaban vs. acenocoumarol</td>
<td>Randomized, open-label</td>
<td>Recurrent thrombosis (arterial or venous)</td>
<td>190</td>
<td>190</td>
</tr>
<tr>
<td>RAPS</td>
<td>02116036</td>
<td>K.J. Legault, MA, Crowther (Canada)</td>
<td>H/o venous thrombosis, currently on anticoagulation</td>
<td>Rivaroxaban 20 mg qd</td>
<td>Single-arm pilot study</td>
<td>Pilot + feasibility study to consent, enroll &amp; follow patients. Secondary outcomes: recurrent thrombosis, bleeding</td>
<td>150</td>
<td>81</td>
</tr>
</tbody>
</table>

**Abbreviations:** APLA, antiphospholipid antibody; APS, antiphospholipid syndrome; GFR, glomerular filtration rate; H/o, history of.

*Not to be confused with another APS study also called “RAPS.” Cohen H et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomized, controlled, open-label, phase 2/3, noninferiority trial. Lancet Hematol. 2016;3:e428-38; this study had laboratory parameters (endogenous thrombin potential) as the primary outcome.

# Stopped early because of funding reasons.

14 The Hematologist: ASH NEWS AND REPORTS
In this plenary paper, the investigators present results from a prospective phase 1b/2 study on the Bruton tyrosine kinase inhibitor ibrutinib in patients in need of salvage therapy for chronic lymphocytic leukemia (CLL). Dr. Miklos D, Catter C, Arora M, et al. ibritunib for chronic lymphocytic leukemia (CLL) treated with ibrutinib in a phase 2 trial. Blood. 2017;130:2420-2430.


In this plenary paper, the investigators present results from a randomized, double-blind study of venetoclax in patients with high-BCL2-expressing tumors and shows that first-line cyclosporine and intrathecal steroids do not add to the therapeutic efficacy of the etoposide-based HLH-94 protocol. Dr. Fazanee Kordbaech and colleagues demonstrate in vitro and in vivo exposure to extracellular histones induces erythrocyte aggregation, increases fragility, and upregulates splenic clearance, potentially explaining acute anemia in the setting of sepsis and other severe illnesses. Kordbaech F, O'Meara CH, Coupland LA, et al. Extracellular histones induce erythrocyte fragility and anemia. Blood. 2017;130:2884-2888.


In this plenary paper, the investigators present results from a prospective phase 1b/2 study on the Bruton tyrosine kinase inhibitor ibrutinib in patients in need of salvage therapy for chronic lymphocytic leukemia (CLL). Dr. Miklos D, Catter C, Arora M, et al. ibritunib for chronic lymphocytic leukemia (CLL) treated with ibrutinib in a phase 2 trial. Blood. 2017;130:2420-2430.

A Man With Hyperleukocytosis and Massive Splenomegaly

1. Resident Pathologist, University of Chicago Medical Center, Chicago, IL
2. Hematopathologist, University of Chicago Medical Center, Chicago, IL

A previously healthy 27-year-old man presented to an outside hospital with bilateral ear aches and prescribed a short course of antibiotics with a working diagnosis of bilateral otitis media. Two weeks later, he presented to an outside hospital emergency department with syncope and was transferred immediately to our hospital for further care. During admission, on physical examination the patient was noted to have palpable splenomegaly. Laboratory tests performed were notable for a white blood cell count of 103.9 \times 10^3/\mu L, hemoglobin of 8.1 g/dL, and platelets of 99 \times 10^3/\mu L. Abnormal circulating cells were present in significant numbers (45%, black arrow; 12%, grey arrow). However, reverse transcriptase–polymerase chain reaction for BCR-ABL detected only very low numbers of both p210 and p190 transcripts. The images shown here are of a Giemsa-stained peripheral blood smear (Figure 1 [low power] and Figure 2 [high power]), hematoxylin and eosin stained bone marrow core biopsy (Figure 3), and CD61 immunostain on core biopsy for megakaryocytes (Figure 4).

What is your diagnosis?
A. Chronic myeloid leukemia in blast phase
B. Chronic myelomonocytic leukemia
C. Mast cell neoplasm consistent with Mast-cell leukemia
D. Ph+ acute myeloid leukemia

For the solution to the quiz, visit The Hematologist online, www.hematology.org/TheHematologist/Image-Challenge.

Dr. Parker and Dr. Venkataraman indicated no relevant conflicts of interest.

MARK YOUR CALENDAR

March
4  ASH Latin American Training Program application due
www.hematology.org/awards
9-10  Highlights of ASH in Asia-Pacific
Bali, Indonesia
www.hematology.org/highlights
15  ASH-AMFDP Award application due
www.hematology.org/awards
23  ASH Clinical Research Training Institute application due
www.hematology.org/awards
30  ASH Medical Educators Institute application due
www.hematology.org/educators

April
6  ASH Visitor Training Program application due
www.hematology.org/awards
24-26  ASH Clinical Research Training Institute
Latin America workshop
Rio de Janeiro, Brazil
www.hematology.org/awards
27-28  Highlights of ASH in Latin America
Rio de Janeiro, Brazil
www.hematology.org/highlights

May
1  ASH Bridge Grant & ASH Global Research Award applications due
www.hematology.org/awards
15-16  NHLBI State of the Science Workshop,
Factor VIII Inhibitors
Bethesda, MD
https://factorviiinhibitors.eventbrite.com
16-20  11th International Congress on Autoimmunity
Lisbon, Portugal
http://autoimmunity.kenes.com

Read The Hematologist online at
www.hematology.org/TheHematologist, and catch up on the latest news in the field of hematology right on your desktop, mobile phone, or tablet.