MSHP Pharmascript

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Welcome New MSHP Officers and Board Members!

Pictured above: Asha Tata, Kelly Harbourt, Jacob Smith, Celia Proctor, Rachel Kruer, Meghan Swarthout

Congratulations and welcome to the new MSHP Officers and Board Members! The following individuals were installed at the MSHP Spring Seminar:

President-Elect: *Rachel Kruer, PharmD, BCPS, CNSC*
Secretary: *Asha Tata, PharmD, BCPS*
MSHP Board Members: *Kelly Harbourt, PharmD, BCPS and Jacob Smith, PharmD, MBA*

A big thank you to the outgoing officers, Past-President, Brian Grover and Board Members, Mehrnaz Pajoumand and Kristin Watson for their service over the past three years.

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MSHP Spring Seminar Highlights

The MSHP Spring Seminar was held Friday, April 8th at The Hotel at Arundel Preserve. The attendees were able to hear great presentations on a variety of topics, review the business of MSHP, and welcome the new officers (pictured above). Some highlights included a morning presentation by Michael A. Evans, BS, RPh, AVP of Strategy and Innovation and Co-Director for the Center for Pharmacy Innovation and Outcomes at Geisinger Health System. This outstanding presentation on MTDM at Geisinger is receiving the ASHP Award for Excellence at the ASHP Summer Meeting in Baltimore. The day ended with a presentation by Patricia C. Kienle, RPh, MPA, FASHP, Director of Accreditation and Medication Safety at Cardinal Health Innovative Delivery Solutions who guided the attendees on what to expect with USP <800>.

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Taking on ASHP Midyear 2015 as a 4th Year Pharmacy Student

Jamie Nguyen, PharmD Candidate 2016

This year, ASHP Midyear 2015 was held in the colorful South of New Orleans, Louisiana. It is a week-long convention where a diverse group of pharmacy professionals and pharmaceutical representatives concentrate in one place to exchange and discuss progress, practice models, research, technology, and patient care. It is also a hub of pharmacy job opportunities. Everyone is dressed smartly and professionally. The stakes feel monumental, as every individual encountered could potentially be a network of pharmacists, hiring pharmacy managers, or residency/fellowship directors. The networking opportunities at Midyear are endless.

As a 4th year pharmacy student, I was interested in residency programs and job prospects. Specifically, I came to Midyear to finalize my list of potential residency programs and focused much of my energy and preparation on the ASHP Midyear Showcase. Advice that I would provide potential Showcase attendees are to bring the following items in advance: a printed map of the booth locations, a list of questions specific for residents, preceptors, and residency directors, a detailed excel sheet of potential programs and their differences, and specific questions for each program. I also prepared copies of my curriculum vitae and business cards although few programs asked me for either. I was informed that some programs keep records of who visited their booth during Midyear and made it a point to visit every program on my list.

As for the Residency Showcase itself, it wasn't quite the monster that I imagined. Certainly, the Showcase was congested and intimidating in a manner that could be easily overwhelming. All of this was true, particularly at highly competitive programs. However, many residents actively sought out and were very inclusive with as many potential candidates as possible. I found that I never waited long before a resident noticed my lingering presence and ushered me into their group of cordial, but rapid-fire, question and answer sessions. As the showcase continued, my initial trepidation disappeared. There wasn't much time to be shy. Notably, some programs scanned badges and asked visitors to sign in; I was informed that some programs may factor this component into their selection process. All in all, I ended the three day session feeling exhausted, a little hungry, but had successfully collected plenty of data to help me differentiate the programs. I ultimately utilized much of what I learned at Midyear to better personalize my cover letter for each program.

The Personnel Placement Service (PPS) available at Midyear provided opportunities for pharmacists and candidates to interview for jobs and residency or fellowship programs. While many participating programs were fellowships or Postgraduate year 2 programs, there were also opportunities for PPS interviews with Postgraduate year 1 programs. I did not utilize any PPS interviews; however, I did learn that some PGY2 programs required a PPS interview during Midyear before considering applicants. For my peers who signed up for the PPS interviews, their experience was even more rigorous. This was especially true for fellowships, as some candidates woke up as early as 5 am to line up for the chance to sign up for interviews, with many going through back to back interviews. Furthermore, since many fellowship applications are due soon after Midyear, it was vital to fellowship applicants to have started applications before Midyear.

Lastly, one of my favorite experiences at Midyear was attending the Exhibit. If the free giveaways and snacks didn't excite me, the opportunity to learn about cutting edge pharmacy delivery technology, information services, and the enthusiasm of the company representatives at the exhibit certainly did. Unexpectedly, I had the opportunity to speak to industry pharmacists in an informal setting and learn about their practice. Furthermore, some company representatives were also actively looking to reach out to potential new hires for pharmacy positions. Once again, the Exhibit provided not only a learning experience, but a networking experience as well.

All in all, my experience at Midyear, while exhausting, was also exciting. There were so many opportunities for learning and networking. I met many of my school's recent graduates who had successfully gone on to do specialty training. Seeing these alumni was a delight and reminded me that pharmacy really is a small world. Moving forward, ASHP Midyear 2015 has been a worthwhile experience.

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Updated Guideline for Antithrombotic Therapy for VTE Disease

Sarah K. Holman, PharmD, BCPS, Kwadwo Amankwa, PharmD, BCPS, Vala Behbahani, PharmD Candidate 2017

The American College of Chest Physicians recently released an updated clinical practice guideline for antithrombotic therapy for venous thromboembolism (VTE) disease (January 2016).[1] There is much discussion regarding the update and questions about the practical implications of the recommended changes. One of the most notable changes in the guideline is the recommendation for preferential use of non-vitamin K antagonist oral anticoagulants (NOAC) over warfarin for treatment of VTE in patients without cancer. This is in contrast to previous guideline recommendations that preferred warfarin to the NOACs, and thus has the potential to significantly alter standard practice. These recommendations do not extend to those with cancer, where low-molecular-weight heparin (LMWH) is still preferred over both vitamin K antagonists (VKA) and NOACs. In addition, the recommendations for treatment duration remain unchanged. The major changes to recommendations from the previous guideline (AT9) are outlined below (*see Box 1*).

Box 1: Key Changes to Recommendations for Antithrombotic Therapy for VTE

- **NOACs are suggested over VKA therapy, and VKA therapy is suggested over LMWH for initial and long-term treatment of VTE in patients without cancer**
- For VTE treated with anticoagulants, placement of inferior vena cava filter is not recommended
- Routine use of compression stockings should not be used to prevent post-thrombotic syndrome in acute DVT
- In patients with subsegmental PE and low risk for recurrent VTE, clinical surveillance recommended; if high risk, anticoagulation is recommended
- If recurrent VTE while on non-LMWH (and compliant/therapeutic), switch to LMWH; if recurrent VTE on LMWH (and compliant), increase dose of LMWH

Review of the Evidence

Previously, AT9 suggested VKA therapy or LMWH over NOACs for long-term management of patients with VTE without cancer due to limited randomized controlled trial evidence, minimal experience, and sparse long-term data. The new guidelines however gives preference to the NOACS over VKA, based on additional evidence accumulated since AT9 was released. All 4 FDA approved NOACs now have data from large Phase III trials comparing NOACS with VKAs for acute and long term treatment for VTE. Clinical endpoints assessed in these trials include all-cause mortality, recurrent VTE, and major bleeding.

Pooled analysis of the RECOVER I and RECOVER II Trials (including 5107 patients) showed no significant differences between VKA therapy and dabigatran in risk of all-cause mortality (RR 1.0, 95% CI: 0.67-1.50), recurrent VTE (RR 1.12, 95% CI: 0.77-1.62) and major bleeding (RR 0.73, 95% CI: 0.48-1.10).[2,3] In the Hokusai VTE study, edoxaban, similarly, was non-inferior to VKA for all-cause mortality (RR 1.05, 95% CI: 0.82-1.33), recurrent VTE (RR 0.83, 95% CI: 0.57-1.21) and major bleeding (RR 0.85, 95% CI: 0.6-1.21).[4] Pooled analysis of the Einstein DVT and Einstein-PE Trials, comparing rivaroxaban to VKA and LMWH (in 8281 patients with active DVT or PE) showed similar risks of all-cause mortality (RR 0.97, 95% CI:0.73-1.27) and recurrent VTE (RR 0.90, 95% CI:0.68-1.2). Major bleeding was significantly lowered in favor of rivaroxaban (RR 0.55, 95% CI: 0.38-0.81).[5,6] The AMPLIFY study results also showed no significant differences in all-cause mortality (RR 0.79, 95% CI: 0.53-1.19) and recurrent VTE risk (RR 0.84, 95% CI 0.6-1.18) between apixaban and VKA. Similar to what was found with rivaroxaban, the apixaban group in AMPLIFY had significantly lower bleeding risk (RR 0.31, 95% CI: 0.17- 0.55) compared to warfarin.[7]

The guideline committees' new recommendations preferring NOACS over VKA treatment for VTE patients without cancer is thus supported by the respective trials of the individual agents. In the absence of head-to-head trials of the NOACS, there is very little basis for safety and efficacy comparisons among the different NOAC agents. The guideline committee thus refrained from endorsing specific NOACs.

In summary, the guideline recommends the NOACs over VKAs due to similar risk reduction of recurrent VTE, less frequent bleeding (especially intracranial bleeding), and more convenience for patients due to less frequent monitoring. There is no preference for a specific NOAC agent and options include dabigatran, rivaroxaban, apixaban, and edoxaban requiring the pharmacist to weigh advantages and disadvantages of each.

Practical Considerations

There are several important differences between the NOACs that should be considered when choosing an agent for management of VTE (*Table 1*). Both dabigatran and edoxaban require 5-10 days of a parenteral anticoagulant during initiation while rivaroxaban and apixaban have been studied alone for initial therapy. In addition, while the risk of bleeding overall has been shown to be lower with NOACs than with VKAs, the rate of gastrointestinal bleeding may be higher with dabigatran, rivaroxaban, and edoxaban, making apixaban the preferred agent in those with a history of GI bleed. Rivaroxaban and edoxaban have the benefit of once daily dosing, while dabigatran is the only NOAC with a specific reversal agent. Finally, there is significant potential for drug interactions with the NOACs (CYP 3A4 or P-glycoprotein substrates) requiring a thorough review of concurrent medications when choosing initial therapy.

Table 1: Factors Influencing NOAC Preference

Factor	**NOAC Preferred**
Reversal agent needed	Dabigatran
Once daily oral therapy preferred	Rivaroxaban*, edoxaban
Parenteral therapy to be avoided	Rivaroxaban, apixaban
Dyspepsia, history of GIB	Apixaban

Rivaroxaban is dosed twice daily for the first 21 days of therapy for VTE

Although there are many potential benefits to the use of NOACs for the management of VTE, there are certainly clinical scenarios that remain in which VKA therapy or LMWH should be considered the first line treatment (*Table 2).*

Low-molecular-weight heparin

For patients with cancer, providers may question whether patients may be initiated on NOACs in order to spare patients daily treatment with a LMWH injection. Unfortunately, there is currently no direct data comparing LMWH to NOACs in this population, and indirect data suggest that LMWH may still be a more effective option. LMWH should also be considered for patients who are pregnant or planning to become pregnant due to reduced potential to cross the placenta.

Vitamin K antagonists

In those with severe renal disease, all of the NOACs and LMWH are inappropriate options due to significant renal clearance and increased risk of bleeding; VKA therapy, therefore, is preferred. In patients with history of poor compliance, VKA therapy should be initiated due to the ability to assess compliance with INR measurements as well as a longer duration of action that is more forgiving of missed doses. While the guidelines do not specifically address morbidly obese patients, these patients would also potentially be good candidates for VKA therapy given the ability to titrate dosing based on INR and limited data regarding pharmacokinetics of NOACs in the morbidly obese.[8] Finally, while many insurance companies now include NOACs on their formularies, VKA may still be a preferred therapy and available at a significantly reduced cost.

Table 2: Factors Influencing Anticoagulant Preference

Factor	Anticoagulant Preferred
Cancer Liver disease/coagulopathy Pregnancy Recurrent VTE while on anticoagulation	Low-molecular-weight heparins
Renal disease (CrCl <30 ml/min)* History of poor compliance Need for reversal agent	Vitamin K Antagonists

Renal dosing is available for enoxaparin, however oral medication preferred for long-term anticoagulation if no other indication (listed above) present for LMWH. Thus, VKAs are the preferred alternative when NOACs contraindicated due to renal disease

Although the updated guidelines provide evidence-based recommendations for the initial and long-term treatment of VTE, clinicians should still consider patient specific factors when selecting a treatment regimen. Furthermore, the lack of data regarding NOACs in certain patient populations, such as the morbidly obese and cancer patients, warrants further investigation and the use of alternative anticoagulant therapy at this time.

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Dalbavancin: A Positive Antibiotic Choice?

Jessica Biggs, PharmD, PGY2 Pediatric Pharmacy Resident, University of Maryland School of Pharmacy

Adult Data

The development of novel antibiotics is essential to combat emerging multidrug-resistant organisms. In May of 2014, the Food and Drug Administration (FDA) approved the use of dalbavancin (Dalvance™) for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSI) caused by susceptible isolates.[1] Similar to vancomycin, dalbavancin is a lipoglycopeptide that interferes with cell wall synthesis by binding to the D-alanyl-D-alanine terminus in the peptidoglycan layer to prevent cross-linking.[1] Dalbavancin has been shown *in vitro* and *in vivo* to be bactericidal against Gram-positive organisms, including *Staphylococcus aureus* (both methicillin-sensitive *Staphylococcus aureus* [MSSA] and methicillin-resistant *Staphylococcus aureus,* [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus.*[1] *In vitro* data also supports dalbavancin's bactericidal activity against vancomycin-susceptible *Enterococcus faecium* and *Enterococcus faecalis*.[1] Dalbavancin is not active against Gram-negative organisms.[1] Dalbavancin exhibits concentration-dependent killing and the antibacterial activity correlates best with the ratio of the area under the concentration-time curve to the minimal inhibitory concentration for *Staphylococcus aureus*.[1,2,3]

Regarding the use of dalbavancin for the treatment of skin and skin structure infections, in a phase 3, randomized, double blind, non-inferiority trial including adults with complicated ABSSI, the clinical success of dalbavancin was found to be non-inferior to that of linezolid (88.9% success rate in the dalbavancin group versus 91.2% success rate in the linezolid group at the test-of-cure visit).[4] Furthermore, in another non-inferiority trial including adults with ABSSI, the authors concluded that

dalbavancin was non-inferior to standard conventional therapy (linezolid-vancomycin) for ABSSI in terms of clinical response at both early time points and at the end of therapy (79.7% early clinical response rate in the dalbavancin group versus 79.8% early clinical response rate in the vancomycin-linezolid group, with similar outcomes for the end of therapy).[5]

To date, dalbavancin only carries an FDA-approved indication for ABSSI; however, data also suggests potential efficacy in catheter-related bloodstream infections.[6] Data from animal models determined that central nervous system (CNS) penetration of dalbavancin is insignificant, likely demonstrating it will not be effective for the treatment of CNS infections, such as meningitis.[7]

The most common adverse drug events associated with dalbavancin therapy include nausea, headache, and diarrhea.[1] Less common, though more serious, side effects include infusion-related reactions, hepatotoxicity, and *Clostridium difficile* infection.[1] Per the package insert recommendations, the manufacturer cautions against hypersensitivity reactions, hepatic effects, infusion-related reactions ("Red-Man Syndrome") and the potential for superinfection.[1] Extreme caution should be used in patients with a known glycopeptide allergy due to the potential for cross-sensitivity.[1]

Dalbavancin is unique not only in its potency and activity against a variety of Gram-positive organisms, but also in its pharmacokinetic parameters. With an extended terminal half-life ranging from 147-342 hours, once-weekly intravenous (IV) administration (1000 mg IV initial dose, followed by a 500 mg IV dose one week later) is acceptable.[1,3,8] Dalbavancin is not a substrate of the CYP-450 pathway and does not require dosage adjustment during hepatic impairment. However, dalbavancin is excreted renally and requires a dosage adjustment in patients with a creatinine clearance less than 30 who are not on dialysis.[1,3,8]

Pediatric Data[9]

While pharmacokinetic data is widely available in adult patients, information regarding pharmacokinetic parameters in pediatric patients has only recently been released. In July of 2015, the Pediatric Infectious Disease Journal published an article by Bradley and colleagues. The purpose of this article, which included ten pediatric subjects, was to establish the pharmacokinetic parameters, safety and tolerability of a single dose of dalbavancin in children aged 12 to 17 years. In this study, patients ≥60 kg (n=5) were administered a 1000 mg dose of dalbavancin, mirroring adult dosing. In children <60 kg (n=5), a dose of 15 mg/kg was administered. This latter dose was chosen based off of a population pharmacokinetic model that was used to predict dalbavancin exposure in this patient population. In both cases, after the dose was administered, blood and urine samples were collected at pre-specified time points and analyzed for dalbavancin concentrations using a high-performance liquid chromatography method. A summary of pharmacokinetic parameters, with a comparison to known adult pharmacokinetic data, is detailed in Table 1.

Table 1

Pharmacokinetic Parameter	Pediatric[9]	Adult[1,3,8]
Approximate area under the curve (mcg•hr/mL)	17,000	25,000
Volume of distribution at steady state (L)	11 – 18	7 – 14
Terminal half-life (hr)	216 – 219	147 – 342

As evident, the area under the curve exposure in this pediatric population was approximately 30 percent less than that documented in adults, which is consistent with the enhanced renal elimination that is usually documented in healthy adolescents as compared to adults. Furthermore, the apparent terminal half-life in this pediatric population was within the reported range seen in adults.

In terms of safety data, reported adverse effects included headache, abdominal pain, dizziness, diarrhea, nausea, and vomiting. One child in each group also experienced a mild elevation in serum bilirubin, which was deemed by the authors to be unrelated to the study drug.

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Logistical Information

Dalbavancin is available as a 500 mg vial and is only compatible in normal saline. It is administered as a 30 minute infusion via a peripheral line. On the manufacturer's website, the Dalvance Connects℠ program is available for assistance to healthcare providers and their patients in transitions of care.[1] The program assists with insurance coverage, as well as locating infusion centers where patients may receive their treatment as an outpatient. They also send phone call reminders to patients about receiving their second dose.

Therapy Concerns

Although the use of dalbavancin for outpatient therapy is attractive given the need for infrequent doses and the avoidance of an indwelling line for prolonged intravenous therapy, there are also potential concerns associated with dalbavancin therapy. First, although the exact price will vary based on an institution's acquisition fee, the cost of dalbavancin, especially compared to standard of care therapies for ABSSI, is high (Table 2). Also, although not reported to-date, dalbavancin's extended half-life raises the concern for the management of allergic reactions and adverse effects if they were to occur in a patient. Last, as the drug concentration wanes in a patient's body, there will be times when this concentration is below that of the minimum inhibitory concentration, which theoretically can lead to the development of resistance. A single IV dose of dalbavancin 1000 mg yields a mean plasma concentration of >35 mg/L, which far exceeds the MIC of dalbavancin for target organisms, for approximately 7 days.[10] Similarly, the FDA-approved dalbavancin regimen of 1000 mg IV, followed by 500 mg IV yields a mean plasma concentration of approximately 30 mg/L in human serum for at least 2 weeks.[10] Using the approximation that it takes about five half-lives for a drug to be eliminated from the human body, dalbavancin's elimination would take anywhere from 30 to 72 days (with a half-life range of 147 to 346 hours).

Table 2

Parameter	Dalbavancin[1,3.8,11]	Telavancin[11]	Oritavancin[11]	Vancomcyin[11]
Typical dose	1000 mg IV on day 1, 500 mg IV on day 8	10 mg/kg IV Q24hr	1200 mg IV x 1 dose	Varies
Approved indication(s), adult	ABSSI	Complicated SSSI, HAP, VAP	ABSSI	Multiple
Dosing frequency (normal renal function)	Weekly (x 2 doses)	Q24hr	Once	Varies – usually multiple times daily
Half-life (adult), hr	147-346	7-9	393	4-8
Protein binding, %	93-98	90-93	86-90	10-55
Renal dose adjustment	Yes, CrCl < 30 mL/min	Yes, CrCl < 50 mL/min	No	Yes
Hepatic dose adjustment	No	No	No	No
Infusion time, min	30	60	180	>30
CYP interactions	No	No	Weak inhibitor?	No
Approximate cost (14 day course for SSSI)[14], $	~5,000	~6,000†	~3,480	~774††

SSSI: skin and skin structure infection; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia
†: Assuming a course for SSSI for a 75 kg patient; ††: Assuming a course of 1 g IV Q12hr x 14 days

At this time, more clinical efficacy information is needed to support the use of dalbavancin in pediatric patients. Also, in both adults and pediatrics, comparative studies of efficacy and safety of dalbavancin against other comparable agents, as well as economic analyses, are required.

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New Drug Update: Daratumumab (Darzalex™)

By Nicole Hollinger, PharmD and Steven Gilmore, PharmD, BCOP, University of Maryland Medical Center

Multiple myeloma (MM) is a progressive and incurable cancer of the blood where malignant plasma cells prevent the bone marrow from producing normal, healthy blood cells. Myeloma cells produce M-protein, an immunoglobulin, which invades and destroys bone tissue.[1] Symptoms of MM may present as bone pain, renal insufficiency, hypercalcemia, anemia, and recurrent infections. The estimated 5-year survival for patients diagnosed with MM in 2011 was 47%. In November 2015, daratumumab (Darzalex™), a novel treatment option for patients with refractory MM, was approved under the Food and Drug Administration's accelerated approval program.[2] Daratumumab is the first human monoclonal antibody approved for use in MM, which has a novel mechanism of action where it binds CD38-expressing myeloma cells and inhibits tumor growth by inducing apoptosis.

The safety and efficacy of daratumumab was demonstrated in two open label phase-2 studies, which enrolled patients with refractory or relapsing MM who had received at least three previous lines of therapy, and were refractory to both a proteasome inhibitor and an immunomodulatory agent. The first trial found that in the 42 patients who received cycles of 16 mg/kg, 36% had a complete or partial reduction in their tumor burden and a median progression-free survival of 5.6 months and 77% surviving at 12-months.[3] In the second study of 106 patients receiving daratumumab, overall response occurred in 29.2% of patients with a median duration of 7.4 months, progression-free survival was 3.7 months, and 64.8% surviving at 12-months. The most common adverse reactions of any grade were infusion-related reactions (42%), fatigue (40%), and anemia (33%).[4] Daratumumab is also currently being studied in phase 3 trials in combination with backbone therapies for both refractory and previously untreated MM.[5]

Daratumumab is administered as an intravenous (IV) infusion at 16 mg/kg per dose of actual body weight once weekly for 8 weeks, then bi-weekly for 16 weeks, and then once monthly until unacceptable toxicity or disease progression occurs. The most common and most serious adverse reactions of daratumumab are infusion-related reactions (eg bronchospasm, dyspnea, hypoxia, hypertension, nasal congestion, chills, and rhinitis) which can be delayed. The infusion rate of daratumumab should be escalated slowly in 50 mL/hour increments each hour according to the product label. Patients receiving daratumumab should be pre-treated to reduce the risk and severity of infusion reactions. An IV corticosteroid, an oral antipyretic, and an oral or IV antihistamine are recommended. Patients should also receive post-treatment with oral corticosteroids to prevent delayed reactions. Daratumumab does not have any drug-drug interactions, but may interfere with serologic testing.[6]

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Pictures of attendees enjoying a networking session at the Spring Seminar

Upcoming Meetings

Board and Committee Chairs Meeting: May 11, 4:00 to 5:30 pm at Johns Hopkins Home Care Group

Board Only Meeting (no Committee Chairs): June 8, 4:00-5:30

Call for Articles

The editors of Pharmascript are seeking article topics related to ASHP recommended Pharmacy Practice Advancement Initiatives, student or resident research, and updates in biologic therapy for treatment of autoimmune diseases. Interested writers are encouraged to submit articles in one of the two clinical contents as a clinical review (1,000 words), a research project manuscript (2,000 words), or a new drug update (250 words). Other article topics will be considered as well. Articles should be submitted via email by July 1st, 2016 to be published in the July edition of MSHP's Pharmascript to Carla Williams: cpeterman@umm.edu or Steven Gilmore: sgilmore@umm.edu.