Volume 26 • Issue 6 www.pswi.org

November/December 2023

The Journal

of the Pharmacy Society of Wisconsin

2023 PSW Annual Meeting

November/December 2023

The Journal
of the Pharmacy Society of Wisconsin

The Journal of the Pharmacy Society of Wisconsin is a professional publication for original research, review, experience, and opinion articles that link science with contemporary pharmacy practice to improve patient care. Together we can inspire each other to advance our profession with the single purpose of enhancing the lives of our patients.

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The Journal of the Pharmacy Society of Wisconsin (ISSN 2837-8229) is the official publication of the Pharmacy Society of Wisconsin. Published bimonthly by the Pharmacy Society of Wisconsin, 701 Heartland Trail, Madison, WI 53717. Opinions expressed by contributors do not necessarily reflect those of PSW.

Features

UpFront:

Leadership Reminders - Creating a Circle of Safety for Your Team Amidst Workforce Challenges

by Hannet Tibagwa Ambord, PharmD, MS, MBA

Family members take care of each other, from birth to old age and at every stage in between. We often create "circles of safety" for our family members (whether that's parents, children, spouses, or siblings) and stand up for them even when they're not in the room.

As Charles Duhigg explains in Smarter Faster Better, his book about productivity, the concept of family members caring for one another extends beyond family dynamics and applies to the relationships between leaders and employees. When employees enter our organizations, they entrust us with their well-being, which makes them invaluable assets. As leaders, we must be willing to advocate for our employees, even when they are not present.

In a time when occupational burnout is rampant and our workforce is traumatized, it's imperative for leaders to cultivate a circle of psychological safety. Team norms should foster an environment where employees feel comfortable taking risks, addressing conflicts openly, building trust, empathizing with one another, expressing enthusiasm for their ideas, and fostering diverse opinions without fear of repercussions. After all, your team's norms and values will become an embodiment of your organizational culture.

Humans naturally desire a sense of control—even babies express this desire by occasionally resisting the activities they need, like sleep. Effective leaders should create an atmosphere that empowers employees to take the driver's seat, signaling support and trust for them. Developing an internal locus of control can enhance staff morale, motivation, and retention.

Amid workforce shortages and increased stress, I look to Rory Vaden, a "self-discipline strategist, for his "focus funnel" time management model to help with work management. First:

- Give yourself permission to eliminate elements that do not add value, such as projects, meetings, and services.
- Delegate whenever possible and where it makes sense. For instance, at Reedsburg Area Medical Center, we regularly enlist retired nurses to assist with our fall immunization efforts, diffusing stress on our retail pharmacy staff.
- Use automation to gain efficiencies.

When elimination, delegation, or automation is not possible, work must pass through the focus funnel. As a task filters through, assess whether staff should handle it immediately or later. Prioritize "now" tasks and intentionally postpone "later" tasks. Intentionally procrastinated work re-enters the focus funnel along with new tasks, repeating the same process. Don't be surprised if some of the intentionally procrastinated work resolves itself.

When we bring new employees on board, they don't arrive with the expectation of being managed; they expect to be led. Effective leadership requires a clear vision, a well-thought-out strategy, and the technical expertise necessary to guide your team. As a caution, never ask an employee to do something you wouldn't do yourself. Keep your ear to the ground and refrain from "managing in abstraction."

Be a mentor by investing time in understanding your team's strengths and weaknesses. Use this knowledge to offer tailored support that helps team members reach their full potential. Empower your team to unlock the innovator within, enabling them to function like a well-oiled machine even in your absence.

Demonstrate a genuine interest in your employees' success and well-being. Invest time in getting to know your employees and their families beyond the workplace—nurture and strengthen these relationships.

Recognize that career development for employees is vital for professional growth and engagement. Investing in employees today will yield benefits for the organization in the future by reducing turnover.

Being results-oriented is crucial. As the late management consultant Peter Drucker reminds us, not everything that is measured needs to be improved. By measuring the right metrics and understanding the value of data, you can make informed decisions.

Finally, embody the traits of a good leader: maintain a passion for your work, be an attentive listener, consistently share information in a timely manner, and foster open and honest communication.

Hannet Tibagwa Ambord is the President of the Pharmacy Society of Wisconsin in Madison, WI.

PHARMACIST & TECHNICIAN CE:

Getting Under the Skin: New Medications for Dermatologic Conditions

by Courtney Quinn PharmD, Deanna Jacobs PharmD, Joyce Hu, 2024 PharmD Candidate, Lindsey Paul, 2025 PharmD Candidate, Anthony Rende, 2026 PharmD Candidate, Drew Vander Velden PharmD, Charisse Yan, 2025 PharmD Candidate, Amanda Margolis, PharmD, MS, BCACP

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Learning Objectives

- Describe the pathophysiology and symptoms of plaque psoriasis, generalized pustular psoriasis flares, and atopic dermatitis.
- Describe the mechanism of action for newly approved dermatologic agents.
- Describe the anticipated place in therapy for newly approved dermatological agents.
- List adverse effects for newly approved dermatological agents.

Plaque psoriasis is a chronic and complex inflammatory disease that predominantly affects the skin. It often presents as inflamed, red, scaly plaques.[1] This condition is caused by uncontrolled keratinocyte proliferation, or adaptive and innate immune system dysregulation or alterations, and primarily involves cytokines tumor necrosis factor alpha (TNF-α), interleukin-17 (IL-17), and IL-23.[2] Generalized pustular psoriasis (GPP) is a rarer variation of the disease that is influenced by a different cytokine pathway and involves a mutation in the interleukin 36 receptor antagonist (IL-36RN).[2,3] Atopic dermatitis (AD) is another chronic inflammatory condition of the skin characterized by episodic flares and periods of remission. Mechanisms involved include epidermal barrier dysfunction, genetics, and dysregulation of the immune system.[4]

Treating these conditions' physical symptoms is crucial because they have the strong potential to affect a person's quality of life.[5] Physical symptoms can also impact the patient's relationships and family. Psychosocial symptoms can arise leading to social avoidance, missing work or school, and economic burdens. These symptoms can lead to mental health disorders such as anxiety and depression.[5,6] Alleviating the physical symptoms can combat some of these possible consequences.

The mainstays of treatment for both psoriasis and AD, particularly for mild disease, are topical medications.[6,7] However, for patients with more severe disease and larger areas of affected body surface area, treatment regimens frequently must incorporate oral systemic therapies or injectable biologics to gain symptom control.[6,8,9] Some patients remain uncontrolled after multiple trials of currently available agents, leading to a demand for the novel treatments discussed in this review. Fortunately, in the past few years, the recent approval of new dermatologic drugs have offered hope. This review will cover six recently approved dermatological medications (Table 1).

Deucravacitinib

Deucravacitinib is the first selective, tyrosine kinase 2 (TK2) inhibitor to receive Food and Drug Administration (FDA) approval in September of 2022 for the treatment of moderate –to severe plaque psoriasis in adults.[10] There are also currently clinical trials investigating its use in other forms of psoriasis, psoriatic arthritis, alopecia areata, Crohn's disease, ulcerative colitis, and systemic lupus erythematosus. TK2 is a member of the janus kinase (JAK) family that mediates signaling of IL-23 and other cytokines involved in immune-mediated inflammatory diseases.[11-13] TK2 binds with either JAK1 or JAK2 to form dimers, which mediate multiple cytokine pathways and transmit signals, respectively. Deucravacitinib works by locking the regulatory and catalytic domains of TYK2 in an inhibitory confirmation. This leads to downregulation of signal transducers and activators of transcription (STATs)

Acronyms

AD - Atopic dermatitis
AhR - Aryl hydrocarbon receptor
BCRP - Breast cancer resistance protein
DRESS - Drug rash with eosinophilia and systemic symptoms
FDA - Food and Drug Administration
EASI - Eczema area and severity index
GPP - Generalized pustular psoriasis
GPPGA - Generalized pustular psoriasis physician global assessment
IL - Interleukin
IL36RN - Interleukin 36 receptor antagonist
IGA - Investigator's global assessment
JAK - Janus kinase
PDE-4 - Phosphodiesterase 4 inhibitors
PASI - Psoriasis Areaand Severity Index
PGA - Physician's global assessment
STATs - Signal transducers and activators of transcription
sPGA 0/1 - Static physician's global assessment
TNF-α - Tumor necrosis factor alpha
TK2 - Tyrosine kinase 2

TABLE 1. Review of Recently Approved Medications for Dermatologic Conditions

Name	Class	Approved for	Dose	Common Adverse Effects	Significant Adverse Reactions
Abrocitinib (Cibinqo™)	JAK inhibitor	Atopic dermatitis	100 mg once daily. May increase dose to 200 mg once daily after 12 weeks	• Infection (35%) • Nasopharyngitis (9-12%) • Nausea (6-15%)	• Cardiovascular/ thrombotic events • Infection • Malignancies
Deucravacitinib (Sotyktu®)	TK2 inhibitor	Plaque psoriasis	6 mg once daily	• Infection (29%) • Upper respiratory tract infection (19%)	Infection
Roflumilast 0.3% cream (Zoryve®)	PDE-4 inhibitor	Plaque psoriasis	Apply once daily	• Diarrhea (3%) • Headache 2%)	Not Applicable
Spesolimab-sbzo (Spevigo®)	IL-36 antagonist	Generalized pustular psoriasis	900 mg via IV once; if flare persists, an additional 900 mg may be given one week later	Infection (14%)	Infection
Tapinarof 1% cream (Vtama®)	aryl hydrocarbon receptor agonist	Plaque psoriasis	Apply a thin layer to the affected area once daily	• Folliculitis (20%) • Nasopharyngitis (11%)	Not Applicable
Tralokinumab-ldrm (Adbry®)	IL-13 antagonist	Atopic dermatitis	600 mg (four 150 mg injections) once, then 300 mg (two 150 mg injections) every other week	Upper respiratory tract infection (24%)	Ocular effects (conjunctivitis)

IL = interleukin; IV = intravenous; JAK = Janus kinase; PDE = phosphodiesterase; TK - tyrosine kinase

via allosteric inhibition of receptor-mediated activation of TYK2. It is not fully understood how the inhibition of TYK2 works to effectively treat adults with moderate –to severe plaque psoriasis. Deucravacitinib comes as a 6-mg tablet that is taken once daily.

The efficacy and safety of deucravacitinib was investigated in POETYK PSO-1 and POETYK PSO-2, which are companion, phase 3 clinical trials that compared deucravacitinib to placebo and apremilast in moderate to severe plaque psoriasis.[11,12] Both were multicenter, randomized, double-blind, double-dummy, placebo, and active-controlled trials that took place over the course of 52 weeks. Participants were included in the studies if they were age 18 or older, had moderate to severe plaque psoriasis for a duration for 6 months or longer, were eligible for systemic treatment or phototherapy, had not received apremilast or deucravacitinib previously, and underwent a washout period if they were receiving treatment with other medications. Patients (n = 1,684) were randomized 2:1:1 to receive deucravacitinib 6 mg every day, placebo, or apremilast 30 mg twice a day. The coprimary endpoints that were assessed at week 16 in both clinical trials were a ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) and static Physician's Global Assessment score of 0 or 1 (sPGA 0/1) with at least a 2-point improvement from baseline. For both trials, deucravacitinib had statistically significant higher response rates than placebo or apremilastfor PASI 75 (PSO-1: 58.4% vs 12.7% vs 35.1%, respectively, p<0.0001 for both comparisons; PSO-2: 53.0% vs 9.4% and 39.8%, respectively, p<0.0001 vs placebo, p =0.0004 vs apremilast) and sPGA 0/1 (PSO-1: 53.6% vs 7.2% vs 32.1%, respectively, p<0.0001 for both comparisons; PSO-2: 49.5% vs 8.6% vs 33.9%, respectively p<0.0001 for both comparisons). Efficacy improved beyond week 16 and was maintained by trial completion. Deucravacitinib was also able to demonstrate improvements in secondary outcomes such as PASI 90, PASI 100, sPGA 0, measures of clear skin and improvements in scalp psoriasis, psoriasis symptoms, and quality of life at higher rates than the placebo and apremilast groups.

As an immunosuppressant medication, deucravacitinib does come with numerous warnings and precautions. It may increase the risk of infections, which could require patients to temporarily discontinue treatment until the illness resolves.[11-13] Because deucravacitinib suppresses the immune system, patients should be evaluated and, if necessary, treated for tuberculosis prior to initiating treatment. Also, the package labeling indicates patients should avoid live vaccines while taking deucravacitinib.[13] During the PSO-1 and PSO-2 trials, there were 3 participants who developed malignancies.[11,12] Elevations in liver enzymes, creatinine phosphokinase, and triglycerides have been observed in patients treated with deucravacitinib.[11-13] Monitoring patients for liver injury and rhabdomyolysis is also necessary. TYK2 inhibition may carry the same risks related to JAK inhibition, which include higher rates of all-cause mortality (sudden cardiovascular death, major adverse cardiovascular events, thrombosis, and malignancies). Currently, the only contraindication for this medication is known hypersensitivity to the agent or its excipients. In vitro, drug interaction studies revealed that deucravacitinib is a substrate of P-glycoprotein, breast cancer resistance protein (BCRP), and organic cation transporter 1, and it is an inhibitor of BCRP and organic anion transporting polypeptide 1B3.

During the 52 weeks of the PSO-1 and PSO-2 trials, adverse events were reported in 74.4% (395/531) and 72.0% (600/833) of participants receiving deucravacitinib and 42.4% (70/165) and 55.3% (277/501) of participants in the placebo group.[11,12]

The most common adverse events for patients receiving deucravacitinib through week 16 in the PSO-1 and PSO-2 trials were upper respiratory infections (19.2%), elevated blood creatine phosphokinase (2.7%), herpes simplex (2.0%), mouth ulcers (1.9%), folliculitis (1.7%), and acne (1.4%).[13] Participants completing 52 weeks of therapy were eligible to enroll in a single-arm, open-label extension trial to further evaluate safety, tolerability, and efficacy with an estimated completion date in July, 2026.[11,12,14] Limited data exists to provide safe recommendations for use in special populations.[13] However, in animal reproduction studies, no effects on embryo-fetal development were observed in rabbits and rats when given doses at least 91 times the maximum recommended human dose. Deucravacitinib was also present in rat milk, which suggests that it would also be excreted in human milk. Safe and effective use in the pediatric population has not been established. For older adult patients (≥ 65 years old), there were higher rates of overall serious adverse reactions, including serious infections, and discontinuations due to adverse reactions through week 16. It appears that efficacy was consistent among all ages studied.

Most patients with mild to moderate plaque psoriasis are effectively treated with topical medications, so the use of deucravacitinib should be reserved for those with moderate to severe plaque psoriasis who are candidates for systemic or phototherapy.[7,13] Also, because this is a newly approved, branded medication, patients will likely need to fail methotrexate, retinoids, cyclosporine, apremilast, and/or immune-modifying, biologic agents. Deucravacitinib should not be used in combination with other potent immunosuppressant medications.[13] The use of combination treatment with a topical medication and deucravacitinib has not been evaluated for safety and efficacy, but dermatologists may decide to also prescribe topical agents. The Journal of American Academy of Dermatology's most recent guidelines were published in 2020, which predates the approval of deucravacitinib.[8]

Tapinarof

Tapinarof 1% cream, sold under the brand name Vtama©, is a topical agent approved for the treatment of plaque psoriasis in adult patients.[15] This medication received FDA approval in May of 2022 and is the first topical, novel, chemical entity launched for the indication of psoriasis in approximately 25 years. Tapinarof is an aryl hydrocarbon receptor (AhR) agonist which downregulates interleukin 17 and promotes skin-barrier protein expression along with antioxidant activity. The specific mechanism of tapinarof related to psoriasis treatment is not known. Tapinarof is available as a 60-gram tube of 1% cream that is applied to affected areas once daily. Tapinarof may be used in all affected areas of the skin, including sensitive areas such as the face, neck, intertriginous areas, axillae, genitalia, inframammary areas, and anal crux.

Tapinarof was studied in two identical, phase 3 randomized, controlled, double-blind trials called PSOARING 1 and PSOARING 2.[16] The trials evaluated tapinarof cream compared to vehicle only for the treatment of mild to severe chronic plaque psoriasis in adult patients over a duration of 12 weeks. The trials included 510 and 515 patients, respectively. Patients were randomized 2:1 to receive either once daily treatment with tapinarof 1% cream or vehicle cream to be applied to existing, new, and resolved lesions for the entire duration of the 12-week trial. Patients were prohibited from using concomitant topical, oral, or injectable medications for the treatment of plaque psoriasis throughout the trial, and they could not receive UV light therapy for the duration of the trial. The primary endpoint in the two trials was the proportion of patients achieving a Physician's Global Assessment (PGA) score of 0 or 1, which indicated clear or almost clear skin. Between the two trials, 35.4% and 40.2% of patients receiving tapinarof reached the primary endpoint compared to 6% and 6.3% of patients receiving the control, vehicle cream, with significantly greater achievement of PGA response in the tapinarof groups in both trials ($p<0.001$ for both comparisons). Key secondary endpoints included the proportion of patients achieving 75% or 90%improvement on the PASI. In the tapinarof groups, 36.1% and 47.6% achieved PASI 75 compared to 10.2% and 6.9% in the control groups ($p<0.001$ for both comparisons). For the endpoint of PASI 90, 18.8% and 20.9% of patients in the tapinarof group achieved this endpoint compared to 1.6% and 2.5% of patients receiving the control ($p<0.001$ for both comparisons).

Tapinarof was also studied in a one-year, open-label, extension trial following the PSOARING 1 and PSOARING 2 trials.[17] The extension trial, PSOARING 3, included patients who had completed the two initial trials, and treatment withtapinarof was provided on an intermittent basis determined by the patient's current PGA score. Patients with a PGA score of ≥ 1 at the start of the trial received tapinarof and were treated until they achieved a PGA score of 0, at which time treatment was discontinued and patients were observed. If disease worsened off treatment (defined as a PGA score ≥ 2), tapinarof was restarted and continued until a PGA score of 0 was reached. A total of 763 patients were enrolled in the trial, 508 of whom had been receiving tapinarof in the previous trial, and 255 of whom had been receiving the vehicle. At baseline, approximately two-thirds of patients had a PGA score of 2 or 3, with the remaining patients primarily having a baseline score of 1. The proportion of patients who achieved complete disease clearance (PGA score of 0) at any time during the trial was 40.9%. Tapinarof was also observed to have a remittive, off-therapy effect, which was defined in the trial as duration of efficacy maintenance with a PGA score of 0 or 1 while off therapy. For patients who achieved a PGA score of 0 at any time during the trial, the mean duration of remittive effect was 130.1 days (Standard Deviation: 89.4 days). The median duration of remittive effect for patients entering the trial with a PGA score of 0 was 115 days. These endpoints were not evaluated for statistical significance due to the lack of an active comparator in this trial.

In terms of safety, tapinarof has no contraindications, warnings, or precautions.[15] There are also no known drug interactions with tapinarof based on in vitro studies. In the PSOARING 1 and 2 trials, adverse events were reported in 50.3% and 54.% of patients receiving tapinarof and 22.4% and 26.2% of patients receiving the vehicle.[16] The most common adverse effects seen in clinical trials were folliculitis which occurred in 20% of patients, along with nasopharyngitis and contact dermatitis which occurred in 11% and 7% of participants, respectively. Across the pivotal

trials, roughly 1%-2% of patients withdrew from the trials due to folliculitis or contact dermatitis. There were no new safety signals identified in the extension trial, and the most frequent adverse event continued to be folliculitis, with 22.7% of patients reporting this adverse event.[17] There is limited data on safety of tapinarof in special populations. There were no overall differences seen in efficacy, safety, or tolerability of tapinarof in elderly patients, and 14.5% of trial participants who received tapinarof were aged 65 or older.

As a new, branded medication, tapinarof's likely place in therapy will be in patients with mild to moderate plaque psoriasis who have failed generic topical therapies such as topical corticosteroids or calcineurin inhibitors. Tapinarof may also be used earlier in treatment for patients with psoriasis in intertriginous areas with psoriasis in intertriginous areas or other sensitive areas where potent, generic topicals are not recommended for use due to potential for skin atrophy. The safety of use in combination with other psoriasis treatment agents has not been evaluated. Providers may choose to use tapinarof in combination with oral systemic agents or injectable biologics in patients with moderate to severe disease. Tapinarof is not currently mentioned in the psoriasis treatment guidelines due to the timing of publication.[8]

Roflumilast

A topical cream formulation of roflumilast (0.3% concentration) was approved by the FDA in July 2022 for the treatment of plaque psoriasis in patients age 12 and older.[18] Roflumilast belongs in the pharmacological class of phosphodiesterase 4 inhibitors (PDE-4) and leads to anti-inflammatory activity, though the exact mechanism of action that exerts its therapeutic effects is unknown. The topical drug is indicated to be applied once daily to areas affected by plaque psoriasis, including intertriginous areas (i.e. skin folds). Currently, its place in therapy is not well established by experts.[19] First-line treatment for mild disease is topical corticosteroids and emollients; for moderate to severe disease, systemic therapies (such as biologics, methotrexate, apremilast, or cyclosporine) are recommended as first-line.[7,8] Given its topical nature and novel pharmacological class, roflumilast may be useful as an adjuvant to first-line treatments in any disease severity.

Despite its undefined place in therapy, topical roflumilast has proven to be effective in treating plaque psoriasis. In two separate phase 3 randomized controlled trials, DERMIS-1 and DERMIS-2, roflumilast 0.3% cream was compared to vehicle cream (placebo), each applied once daily to affected areas for 8 weeks in both studies.[20] The primary efficacy outcome measured in these studies was whether the investigator's global assessment (IGA) success was achieved. IGA is assessed on a 5-point scale of plaque severity from 0 to 4 (0 indicating clear, 4 indicating severe disease). Treatment was considered an IGA success if the patient reached clear or almost clear plaque status at 8 weeks as well as had at least a 2-point improvement from their baseline IGA score. In both studies, roflumilast 0.3% cream was found to be statistically significantly superior to placebo at inducing successful treatment. DERMIS-1 saw 42.4% of their roflumilast-treated participants achieve IGA success, as opposed to 6.1% of the placebo group, resulting in a 39.6% (95% CI, 32.3-46.9%, p<0.001) increase in success rate . Likewise, DERMIS-2 saw a 28.9% (95% CI, 20.8-36.9%, p<0.001) increase in success rate between roflumilast and placebo, with success in 37.5% and 6.9% of patients, respectively.[20]

As for side effects, topical roflumilast has been found to be a very tolerable medication due to the lack of systemic absorption. The most commonly reported side effects were diarrhea and headache, though the prevalence of these adverse effects are 2% and 3%, respectively.[18] Additionally, prevalence of topical irritation resulting from roflumilast cream is low and very comparable to that of placebo vehicle cream; 98.6% of roflumilast-treated patients and 98.4% of placebo-treated patients reported no signs of skin irritation at 8 weeks of treatment.[20]

At this time, further research is needed to determine topical roflumilast 's place in therapy compared to other active treatments as well as long-term efficacy and side effects. Current data lends support to the idea that topical roflumilast has potential to gain a much larger role in the treatment of plaque psoriasis, especially in intertriginous areas. Skin in these areas tend to be thinner and more sensitive and more prone to adverse effects, making roflumilast cream a desirable option given its confirmed efficacy and favorable safety profile.

Spesolimab

Generalized Pustular Psoriasis

GPP is an inflammatory condition characterized by recurrent or persistent flares of pustules and erythema.[21] Although GPP is distinct from plaque psoriasis in its underlying pathophysiology, the two can co-occur in a single patient. GPP is a rare form of psoriasis, constituting approximately 1% of all psoriasis diagnoses.[22]

Both genetic and environmental factors are involved in the etiology of GPP.[22] The genes that are implicated in the development of GPP are typically those involved in innate immunity. Although many mutations have been implicated, the most common is a loss-of-function mutation in the IL-36RN gene which affects IL-1 family cytokines and produces a state of heightened inflammation. Both patients with GPP and plaque psoriasis display increased levels of IL-36, with levels being even higher in GPP.

Although the hallmark of GPP is widespread pustules, systemic symptoms can also accompany the cutaneous manifestations and may include fatigue, nausea, or fever.[21,23] Flares can be idiopathic or linked to a trigger, such as infection, stress, or certain medications. One of the most common medication-related causes of flares is withdrawal from systemic corticosteroids.[21] GPP flares can be deadly, with an estimated 3%-7% mortality rate per flare.

Data supporting GPP treatments is sparse. Since GPP is more commonly seen in Asian patients, much of the available information comes from other countries.[22] In particular, Japan has multiple approved therapies for GPP, including adalimumab, infliximab, certolizumab, secukinumab, ixekizumab, brodalumab, risankizumab, and guselkumab, whereas Europe and the United States had no approved therapies before spesolimab.[21]

Spesolimab

Spesolimab-sbzo is the first drug in the United States with a labeled indication for GPP, gaining FDA approval for the treatment of GPP flares in adults in

September 2022.[24] Spesolimab is an IL-36 antagonist that blocks pro-inflammatory signaling downstream of the IL-36 receptor, although it is not known precisely how this translates to its efficacy in GPP flares. This represents a different mechanism of action from GPP agents approved in other countries, which include inhibitors of TNF-α, IL-17, IL-17R, and IL-23.[25] Spesolimab is administered as a single 900 mg dose, infused intravenously over 90 minutes, although the dose may be repeated after a week if symptoms of the GPP flare persist.[24]

Spesolimab was approved based on data from the phase 2 Effisayil-1 trial.[25] Since spesolimab was designated as an orphan drug by the FDA, no phase 3 trial was performed prior to approval.[26,27] Effisayil-1 was a randomized, double-blind, placebo-controlled trial, enrolling 52 patients aged between 18 and 75 who were experiencing a moderate to severe GPP flare.[25] Patients were excluded if they had a flare requiring intensive care or if they were on concomitant therapy with methotrexate, cyclosporine, or retinoids. Once enrolled, patients were assigned in a 2:1 ratio to receive either a single 900 mg infusion of spesolimab or placebo, with patients stratified based on Japanese ethnicity. To assess outcomes, the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) scoring tool was used. The GPPGA scale assigns a score of 0 to 4 in the categories of erythema, pustulation, and scaling, with 0 being the least severe and 4 being the most severe. For example, a score of 0 in the pustulation subcategory indicates that the patient has no visible pustules, whereas a score of 4 indicates a high density of coalescing pustules. The scores from the three subcategories are then averaged to calculate a final score. The primary endpoint of this trial was achieving a score of 0 in the GPPGA pustulation subcategory, and a key secondary outcome was achieving a total GPPGA score of 0 to 1. Both of these outcomes were assessed at the end of week 1, as patients from both the spesolimab and placebo groups were eligible to receive an open-label dose of spesolimab on day 8 if they were still experiencing symptoms; therefore, any outcomes measured beyond that point were considered exploratory. At the end of week 1, 54% of patients receiving spesolimab achieved a GPPGA pustulation subscore of 0, compared to 6% of patients in the placebo group (difference = 48%, 95% CI: 21 to 67%, p<0.0001). Furthermore, 43% of patients receiving spesolimab achieved a total GPPGA score of 0 to 1, compared to 11% of patients in the placebo group (difference = 32%, 95% CI: 2 to 53%, p=0.02). Based on this data, the investigators concluded that spesolimab led to significant improvements in pustulation at one week. However, this trial is limited by its small sample size and its inability to track efficacy outcomes beyond one week.

Effisayil-1 was also the main trial used to assess the safety of spesolimab.[25] By the end of week 1, 66% of patients in the spesolimab group experienced an adverse event, with 6% having a serious adverse event, whereas 56% of patients in the placebo group had an adverse event, with none having a serious adverse event. Most notably, the rate of infection at the end of week 1 was higher in the spesolimab group than the placebo group at 17% and 6% respectively. Adverse events were also assessed at 12 weeks, although at this point in the trial patients were no longer blinded and the majority (49/52 patients) had received at least one dose of spesolimab. At week 12, 82% of patients who had received any doses of spesolimab, including those originally assigned to the placebo group, had an adverse event, with 12% having a serious adverse event and 47% having an infection. In patients with infection, there was no predominance in causative pathogens or areas of the body affected. By week 12, one patient reported possible drug rash with eosinophilia and systemic symptoms (DRESS), although this diagnosis could not be confirmed. Given the increased risk of infection in patients who receive spesolimab, the package insert warns against using spesolimab in patients with active infection.[23]

Since spesolimab is the only FDA-approved treatment for GPP in the United States, it may emerge as a first-line therapy for this rare disease.

Abrocitinib

Abrocitinib is an oral medication that was approved by the FDA in February 2023 for moderate –to severe AD treatment in patients who are 12 years or older.[28] Abrocitinib is a JAK inhibitor, which is a small-molecule ligand that reversibly inhibits adenosine triphosphate. The inhibition prevents the signaling of multiple cytokines, including, but not limited to, IL-4, IL-13, and thymus- and activation-regulated chemokine, which are involved in the development and progression of AD.[28,29] Abrocitinib is mainly metabolized by liver enzymes, with both the parent drug and its metabolites having JAK inhibition activities. The recommended starting dose for abrocitinib is 100 mg orally once daily, which can be increased to a maximum dose of 200 mg orally once daily if there is an inadequate response at 12 weeks.[28] However, it is recommended to discontinue abrocitinib if therapy is not effective at its maximum dose.

Abrocitinib is recommended for use in patients who have uncontrolled, moderate –to severe AD who have failed or have contraindications to other systemic therapies including biologics.[28] The efficacy of abrocitinib was evaluated in the JADE-MONO-1 trial, a randomized, double-blind, multi-center phase 3 trial conducted in patients 12 years or older with moderate to severe plaque psoriasis, where abrocitinib 100 mg and 200 mg were compared to a placebo.[30] The primary efficacy endpoints in this trial included the proportion of patients who achieved a 5-point IGA response with a 2 or more point improvement from baseline at 12 weeks, and the proportion of patients who achieved a 75% or more improvement in Eczema Area and Severity Index (EASI) score from baseline at 12 weeks. In regard to the IGA response, there were statistically significantly higher proportions of patients who achieved a 2 or more point A 2 or more point improvement from baseline at 12 weeks in the abrocitinib 100 mg and 200 mg groups when compared to the placebo group, with a 15.8% (95% CI of 6.8%-24.8%, p=0.0037) and 36.0% (95% CI of 26.2%-45.7%, p<0.0001) increase respectively. In regard to the EASI-75 response, there were statistically significantly higher proportions of patients who achieved at least 75% improvement in EASI score at 12 weeks in the abrocitinib 100 mg and 200 mg groups when compared to the placebo, with a 27.9% (95% CI of 17.4%-38.3%, p<0.0001) and 51.0% (95% CI of 40.5%-61.5%, p<0.0001) increase respectively. The investigators concluded that abrocitinib dosed at 100 mg and 200 mg once a day is effective in treating moderate –to severe AD

as monotherapy. However, due to the short study period of only 12 weeks, the long-term efficacy of abrocitinib in controlling AD is uncertain.

Abrocitinib can be used together with topical corticosteroids if needed, but it is not recommended to use in combination with other JAK inhibitors, biologic immunomodulators, or other immunosuppressants.[28] The JADE MONO-1 phase 3 trial also examined the safety of abrocitinib at once-a-day doses of 100 mg and 200 mg.[30] The most frequently reported side effects were nausea (placebo = 3%, abrocitinib 100 mg = 9%, abrocitinib 200 mg = 20%), nasopharyngitis (placebo = 10%, abrocitinib 100 mg = 15%, abrocitinib 200 mg = 12%), and headache (placebo = 3%, abrocitinib 100 mg = 8%, abrocitinib 200 mg = 10%). Serious adverse events including chronic inflammatory bowel disease and acute pancreatitis were observed with an incidence of less than or equal to 4% among both the intervention groups and placebo group. However, the patients recovered after permanently discontinuing the medication. Death was not observed in any of the study groups during the study period; however, abrocitinib still carries a warning regarding increased mortality including sudden cardiovascular death based on research from other JAK inhibitors.[28,30] The JADE MONO-1 investigators concluded that abrocitinib dosed at 100 mg and 200 mg once a day is tolerable and safe for patients to use.[30] However, as with the efficacy data, it is unclear whether abrocitinib is safe for long-term use due to the short study period of 12 weeks.

Tralokinumab

Tralokinumab is a newly approved drug used for the treatment of moderate –to severe atopic dermatitis (AD). Tralokinumab is a monoclonal antibody that works as an IL-13 antagonist. IL-13 is thought to be an important factor in the pathophysiology of AD, as increased expression of the cytokine is found in AD lesions on human skin.[31] Binding of IL-13 to its receptor in the body results in a signal transduction pathway. This pathway decreases the amount of stratum-corneum strengthening molecules such as ceramides and filaggrin, and it increases the amount of proinflammatory proteins.[32] Overall, greater activation of the IL-13 receptor leads to the weakening of the stratum-corneum, which allows for more allergens and bacteria to enter the skin, resulting in a more severe disease state. Tralokinumab works to treat AD by tightly binding to IL-13, so the cytokine cannot bind to its receptor and initiate its signaling cascade.

The drug is currently formulated as a subcutaneous injection available for patients in a prefilled syringe containing 150 mg of the drug. Tralokinumab is first given as a 600 mg loading dose, and then 300 mg doses are administered every other week for maintenance. If a patient weighs less than 100 kg and is able to achieve clear or almost clear skin after 16 weeks of using the therapy, 300 mg can then be administered every 4 weeks.[31]

Clinical trials for tralokinumab tested the efficacy of the drug by using the primary endpoints of proportion of patients who achieved an IGA score of 0 (clear skin) or 1 (almost clear skin) and the proportion of participants who achieved EASI 75.[33] In the randomized, double-blinded, phase 3 trials ECZTRA 1 and ECZTRA 2, subjects with moderate –to severe AD were assigned to receive either 300 mg of subcutaneous tralokinumab every 2 weeks or placebo. There was a statistically significant increase in the proportion of participants with an IGA score of 0 or 1 in those receiving the drug versus placebo in both trials. In ECZTRA 1, 15.8% of patients receiving tralokinumab achieved an IGA score of 0 or 1 after 16 weeks of therapy and only 7.1% of patients receiving placebo achieved this endpoint (MD: 8.6%, 95% CI 4.1-13.1%, p=0.002). In ECZTRA 2, 22.2% of tralokinumab patients and only 10.9% of placebo patients achieved this endpoint after the 16 week trial (MD: 11.1%, 95% CI 5.8-16.4%, p<0.001).[33] The tralokinumab group also had a statistically significant increase in the proportion of patients achieving EASI 75 after 16 weeks of therapy. In ECZTRA 1, 25.0% of tralokinumab patients and 12.7% of placebo patients achieved this endpoint (MD: 12.1%, 95% CI 6.5-17.7%, p<0.001), and in ECZTRA 2, 33.2% of tralokinumab patients and 11.4% of placebo patients achieved this endpoint (MD: 21.6%, 95% CI 15.8-27.3%, p<0.001) at the end of the trial.[33] The ECZTRA 3 trial was another randomized, double-blinded trial comparing 300 mg tralokinumab every 2 weeks along with topical corticosteroids versus placebo and topical corticosteroids.[34] In ECZTRA 3, 38.9% of tralokinumab patients and 16.2% of placebo patients achieved an IGA score of 1 or 0 (MD: 12.4%, 95% CI 2.9-21.9, p=0.015). Additionally, 56.0% of tralokinumab patients and 35.7% of placebo patients achieved an EASI 15 at the end of the ECZTRA 3 trial(MD: 20.2%, 95%CI 9.8-30.6, p<0.001).[34] The most frequent adverse events occurring in ECZTRA 1, 2, and 3 were similar. Patients taking tralokinumab reported experiencing viral upper respiratory tract infection (23.1%, 8.3%, 19.4%), conjunctivitis (7.1%, 3%, 11.1%),and headache (4.7%, 2.7%, 8.7%).[33,34]

Tralokinumab should be used in adults with moderate –to severe atopic dermatitis after failure of topical corticosteroids with appropriate adherence and avoidance of triggers.[35] Dupilumab is currently the biologic drug of choice for AD due to its promising safety and efficacy data, and the comfortability of clinicians prescribing it. Tralokinumab is new to the market, and its exact place in therapy compared to similar biologics, such as dupilumab, is currently unknown but will become clearer as it is prescribed to a larger number of patients. As seen from the phase 3 clinical trials, tralokinumab could be used as monotherapy or in combination with topical corticosteroids.[33,34]

Conclusion

In conclusion, the treatment of psoriasis and atopic dermatitis has and will continue to advance. These newly approved treatments and their novel mechanisms of action introduce potentially promising treatment options for patients dealing with these inflammatory dermatological conditions. Having more treatment options may allow refractory patients to find a treatment that helps them gain disease control and improve their quality of life. However, as is the case with any new-to-market medications, post-market surveillance will be crucial to assessing their long-term effects and use in special populations. In the future, there is potential for these drugs to be approved for other indications, as these treatments are being studied for other disease states. For example, Tapinarof has reached phase three trials for

use in atopic dermatitis.[36] The treatment of dermatologic diseases is ever evolving, and clinicians will need to continue to closely monitor for new drug approval and expanding indications to best serve patients.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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Assessment Questions

1. Which of the following is a common comorbidity among patients with dermatologic conditions, such as psoriasis?
   a. Asthma
   b. Benign prostatic hyperplasia
   c. Depression
   d. Epilepsy

2. Which of the following statements are correct about GPP?
   a. Withdrawal of corticosteroids is a common cause of flares
   b. Spesolimab is the first FDA-approved treatment for GPP
   c. GPP constitutes approximately 15% of all psoriasis diagnoses
   d. During GPP flares, patients may experience systemic symptoms like fever, fatigue, and nausea

3. What is the mechanism of action for abrocitinib?
   a. IL-36 antagonist
   b. JAK inhibitor
   c. Phosphodiesterase 4 inhibitor
   d. tyrosine kinase 2 inhibitor

4. Which of the following medications may be especially useful for patients with plaque psoriasis in intertriginous areas?
   a. Abrocitinib
   b. Decuravacutunib
   c. Topical roflumilast
   d. Tralokinumab

5. When is abrocitinib recommended for use?
   a. Uncontrolled moderate-to-severe atopic dermatitis who have failed or have contraindications to other systemic therapies including biologics
   b. As it is the only agent approved by the FDA for generalized pustular psoriasis and therefore is expect to emerge as a first line agent
   c. It is expected to be used as a first-line treatment for mild-to-moderate atopic dermatitis
   d. Second-line treatment of plaque psoriasis, especially in intertriginous areas

6. Which of the following adverse effects is of concern for spesolimab?
   a. Acute pancreatitis
   b. Diarrhea
   c. Headache
   d. Infection

7. Which of the following is a warning that all JAK inhibitors carry?
   a. Acute pancreatitis
   b. Cardiovascular death
   c. Hyperlipidemia
   d. Pruritus

8. For patients taking decravacitinib, what should they do in the case of an infection?
   a. Discontinue decravacitinib and trial a new medication, it is too dangerous to continue
   b. Discontinue decravacitinib until the illness resolves at which time decravacitinib can be restarted
   c. Continue decravacitinib without concern for the infection, it should have no impact
   d. Increase the dose of decravacitinib, it will help treat the infection

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Original Work

A Financial Analysis of Pharmacist Interventions for Patients Using Self-Administered Biologics in a Centralized Specialty Medication Clinic at a Veteran's Affairs Hospital

by Ryan Simonet, PharmD, Jacob Richie, PharmD, Ellina Seckel, PharmD, BCACP, DPLA, Andrew Wilcox, PharmD, DPLA, Amanda Margolis PharmD, MS, BCACP

Abstract

Objective: A centralized specialty medication management (CSMM) clinic led by clinical pharmacy practitioners (CPPs) was implemented to address gaps in patient education, improve home-use of biologic medications, enhance patient safety, and contain costs. The CSMM CPPs completed medication counseling and disease-specific monitoring for patients prescribed any of the 12 specialty medications over the first year of therapy.

Objective: To determine the cost avoidance due to CPP interventions from a CSMM clinic at a Veterans Affairs hospital.

Methods: Patients who completed at least one encounter with the CSMM clinic within the first 13 months of service were included in this retrospective review. Chart review was conducted on included patient encounters, including CPP interventions that were documented and categorized. Estimated costs were determined through literature review and the VA National Acquisition Center drug contract prices.

Results: 73 patients were included with 251 unique documented encounters. Overall, 103 CPP interventions were documented, of which 13 interventions (12.6%) had cost avoidance implications. The CSMM CPPs' interventions resulted in an overall cost avoidance of $57,432 for the evaluation period. The intervention type with the greatest cost avoidance was replacement of products ($22,511), followed by therapy changes and dose corrections. The cost avoidance related to CPP interventions was 149% compared to the cost of the pharmacist to run the clinic (0.2 full time equivalent CPP salary and benefits).

Conclusion: A CSMM model for patients initiating a specialty medication can effectively lead to health-system cost avoidance through CPP-led interventions.

Specialty medications associated with high cost continue to be a focal point in many public and private health system pharmacies' strategic priorities for reducing cost.[1] Specialty medications account for 49.4% of prescription expenditures in 2021 with self-administered subcutaneous biologic medications contributing significantly due to rising drug spend.[2,3] Many private health systems utilize their own integrated specialty pharmacies to retain prescriptions and revenue associated with these medications.[4-6] These specialty pharmacists have been shown to increase medication adherence[4,6], improve medication safety[7,8], and contain costs for both patients and health systems.[6,9,10] The United States Department of Veterans Affairs (VA) does not have its own specialty pharmacy, and these medications are dispensed either from local sites or Consolidated Mail Outpatient Pharmacy (CMOP), the VA Mail Order Pharmacy.

The William S. Middleton Memorial Veterans Hospital and Clinics (the "Madison VA") utilizes clinical pharmacy practitioners (CPP) in select specialty clinics integrated with scheduling, nursing, and physician teams. Within these specialty clinics, many high-cost, subcutaneous specialty medications are prescribed. Prior to January of 2020, specialty clinics had not had a streamlined approach to ensure every patient received thorough initial education on their injectable biologic medication.[11] In addition, specialty CPPs have limited hours dedicated to specialty clinics and may not have adequate time to provide real-time, initial teaching on a newly prescribed specialty medication. In specialty clinics where there is not a CPP present, a nurse or other health care team member provides initial teaching, which also varies based on the clinic and available staff. Initial medication orders and refills are primarily dispensed through CMOP. Once these medications are initiated, they are subsequently monitored with follow-up at their next specialty clinic visit.

The innovative CPP-led video- and telephone-based Centralized Specialty Medication Management (CSMM) Clinic was implemented in January of 2020 to improve patient education, optimize medication use, enhance patient safety, and decrease costs through increased touchpoints with the CPP.[11] Within the CSMM clinic, patients who are prescribed a specialty medication complete an initial teaching during a VA Video Connect (VVC) or phone visit and then follow up after 2 weeks of therapy and at 3, 6, and 11 months post-initiation. The 2-week follow-up focuses on medication tolerability, self-injection technique, and storage. Subsequent follow-ups also include medication efficacy and adherence. Since its creation, the CSMM clinic has expanded from its initial 4 specialty medications and 3 specialty clinics to include 12 specialty medications and allergy, cardiology, dermatology, gastroenterology, and rheumatology specialty clinics. At the time of this review, the clinic was staffed with two 4-hour half-day clinics (i.e. 0.2 CPP FTE [full time equivalent]), and the following medications were monitored by the clinic: abatacept, adalimumab, alirocumab, benralizumab, certolizumab, dupilumab, etanercept, evolocumab, ixekizumab, omalizumab, secukinumab, and ustekinumab. The purpose of this evaluation was to determine the cost avoidance due to CPP interventions from a CSMM clinic at a VA hospital.

Methods

A retrospective chart review was conducted to identify outcomes from the CPP in the CSMM clinic to estimate cost avoidance. Cost assumptions were determined based on literature regarding disease control, cost of medications, and pharmacist salary. The primary outcome was the cost avoidance at the health-system level.

Chart Review

A chart review was conducted on all patients followed by the CSMM clinic from January 2020 through February 2021. Patients were included if they had their initial CSMM visit by November 15, 2020, to allow for at least 3 months of data and appropriate intervention capturing. When an intervention with a cost implication made by a CPP was identified, information was abstracted from the medical record to estimate cost avoidance. Interventions with the potential for cost avoidance but without literature to assign a cost were excluded. An example of an intervention with potential cost avoidance that did not have identified cost for this evaluation was therapy for the management of injection site reactions. It could not be guaranteed that the patient would have switched to another agent, or that the patient's utilization of the medication would have been affected without the CPP intervention.

In cases where cost avoidance could be assigned, the following information was collected: medication, intervention type, refills until next specialty provider appointment, and a qualitative description of the scenario. The number of refills until the next specialty provider appointment was used to determine when the next likely opportunity would have occurred to make the same intervention. This was assumed to be the minimum duration the cost difference would have occurred.

The intervention types included dose correction or device change, therapy change, disease state management, and product replacement. A dose correction or device change intervention was when the CPP intervened on incorrect doses or improper dosing frequency (often due to patient misunderstanding). Disease state management resulted when increased touchpoints/appointments with the CPP enabled a patient to achieve disease state control, or identified the need to change medications sooner than without CPP touchpoints. Disease state control was identified through documented provider assessments in the electronic medical record. These CPP visits often identified allergic reactions or non-responders to therapies, thus accelerating the time to switch biologics and the time to achieve disease state remission.

Literature Search

To evaluate the cost avoidance potential of CPP interventions in a specialty medication management setting, a literature search was performed. Under the assumption that CPP interventions would lead to improved chronic disease outcomes, the search was designed to evaluate cost avoidance associated with disease control. PubMed was searched in February of 2021. There were no limits to the date of publication. Four separate searches were conducted, aimed at retrieving articles of four disease states that were commonly managed by specialty CPPs, including rheumatoid arthritis, psoriasis, inflammatory bowel disease, and ankylosing spondylitis. The following search terms were used:

1. cost AND ("treatment failure" OR "uncontrolled" OR "failure to respond") AND "rheumatoid arthritis"
2. cost AND ("treatment failure" OR "uncontrolled" OR "failure to respond") AND ("Crohn's" OR "inflammatory bowel disease" OR "ulcerative colitis")
3. cost AND ("treatment failure" OR "uncontrolled" OR "failure to respond") AND ("psoriasis" OR "psoriatic arthritis")
4. cost AND ("treatment failure" OR "uncontrolled" OR "failure to respond") AND "ankylosing spondylitis"

Articles were selected if they had cost outcome data for both uncontrolled disease and controlled disease groups. From the literature review, the financial outcomes identified to track included: dose correction and device changes, product replacement, disease state control, and therapy changes. For each of these interventions, the cost of medications was determined utilizing the VA National Acquisition Center Contract Catalog Search Tool.[12]

Cost Determination

To calculate cost avoidance for dose correction or device change and therapy change interventions, the number of monthly refills impacted by the intervention was determined and multiplied by the normal acquisition cost of the drug product [i.e., cost = (# of months) x (Δ med cost)]. For example, if a device was changed and it was determined to be cost avoidant by $100 per month, and it was determined that there were 3 months between the CSMM appointment to the next specialty provider appointment, the total cost avoidance would be $300. Cost avoidance due to disease state management was determined through the literature review by identifying the medical costs of uncontrolled disease

states when compared to well-controlled disease states.[13-15] Again, the cost difference was determined by the number of refills from when the CPP intervened and their next scheduled specialty appointment. The difference in cost between the new medication and discontinued medication was calculated and multiplied by the number of refills. This was added to the amount saved by achieving disease state control per month based on the literature (Table 1) [i.e., cost = (# of months) x (Δ med cost) + ($ disease state control)]. As no literature was found related to ankylosing spondylitis, it was assumed the total all-cause medical cost would be similar to rheumatoid arthritis.

When medications were reported to malfunction or break, or patients stored products incorrectly and the CSMM CPP was able to facilitate acquiring replacement products from the manufacturer at no cost to the patient or the VA, it was assumed the intervention resulted in a direct cost avoidance of the normal acquisition cost of the product to the health system. There were no cost adjustments made for inflation.

Analysis

Cost avoidance was calculated for each intervention and summed to find a total over 14 months. This was averaged to determine a mean annual cost avoidance. The mean annual cost avoidance was compared to the cost of staffing the clinic at current FTE levels to determine an annual return on investment (ROI). The University of Wisconsin-Madison Health Sciences Institutional Review Board self-certification tool determined that the evaluation was not required to undergo IRB review, as this project did not meet the federal definition of research and was undertaken for programmatic evaluation.[16]

Results

There were 73 patients seen by the CSMM clinic during the 14 months following clinic implementation. There were 251 unique encounters evaluated (i.e., appointments), averaging 3.4 encounters per patient. Of the 103 total CPP interventions identified, 19 (18.4%) had potential cost implications. Of those, 13 interventions (12.6% of total interventions) were able to have a cost difference assigned to them based on the literature and cost of medications adjusted (Table 2). The medications with cost differences assigned were adalimumab, abatacept, benralizumab, certolizumab, etanercept, ixekizumab, secukinumab, and ustekinumab.

TABLE 1. Cost Assumptions for Disease State Control

Disease State Control	*Cost Savings Per Month*	*Mean All Cause Medical Cost Savings from Cited Source*
Psoriasis[13]	$115.58	$1387 per year
Rheumatoid Arthritis/Ankylosing Spondylitis[14]	$476.67	$5720 per year
Irritable Bowel Diseases[15]	$1260.08	$15121 per year (excluding pharmacy cost)

TABLE 2. Cost Avoidance of the Centralized Specialty Medication Management Service

Cost Category	*Number of Interventions*	*Cost Avoidance*	*Example intervention*
Replacement Product	4	$22,511	Medication device came with needle guard triggered. CPP managed medication replacement with manufacturer.
Therapy Change	4	$21,390	Medication lost efficacy and next provider appointment was in 3 months. CPP stopped refill transmission and collaborated with provider to trial new medication.
Dose Correction	2	$13,075	Patient unaware of need to start lower maintenance dosing.
Disease State Management	3	$456	CPP facilitated change in medication prior to specialty appointment and patient achieved disease state improvements.
Total Cost Avoidance (14 months)	**13 cost saving interventions**	**$57,432**	
Cost Avoidance (1 year average)	**10.2 cost saving interventions per year**	**$49,228**	

CPP = clinical pharmacy practitioner

The largest cost avoidance category was replacement products, followed by therapy changes and dose corrections. For disease state management, one intervention was found for each of the following disease states: ankylosing spondylitis, Crohn's disease, and plaque psoriasis. There were 2 CSMM CPP therapy changes that resulted in an increased cost ($1,837) due to the CPP recommending a more expensive medication. However, overall, the CSMM CPPs' interventions resulted in a cost avoidance of $57,432 over the first 14 months of the clinic (Table 2). When averaged for a 12-month span, the 1-year cost avoidance was $49,228. This equates to $4,418 per cost-related intervention and $787 per patient.

To calculate the primary outcome, a Level 1 GS-13 CPP salary was used with an assumed 30% additional included for benefits. When adjusted for 0.2 CPP FTE, which is what was needed to maintain the CSMM clinic at the time, the cost was $33,060 annually. When compared to the clinic cost avoidance of $49,228, this resulted in a positive 0.49 return on investment over 1 year (i.e., [49,228-33,060] / 33,060 = 0.49).

Discussion

This retrospective review found a positive ROI of 0.49 as the cost avoidance following the implementation of the CSMM clinic was greater than the cost to run the clinic. This cost avoidance is focused on the health-system and pharmacy department budgets and can be re-allocated to improve care for Veteran patients. Typically, the financial

benefits for specialty pharmacies are described by the revenue and prescription capture rates the specialty pharmacy achieves.[4,6,17] In this case the CSMM clinic was able to demonstrate a positive ROI based on cost avoidance through pharmacist interventions which minimized cost. This supports that there is also a cost avoidance from specialty pharmacist interventions separate from the revenue generated.[9,10]

The cost avoidance findings in this evaluation were modest compared to the two other studies that have evaluated the financial implications of specialty pharmacists' interventions in a health-system setting.[9,10] Compared to Lankford et al, who described the cost implications of health-system specialty pharmacist interventions, this evaluation had a lower proportion of patients with cost avoidance interventions made (34% compared to 12.6% in this evaluation).[9] However, Lankford et al reported a lower cost savings of $2,757 per intervention, whereas this evaluation estimated $4,418 saved per intervention. Soni et al described the cost implication of health-system specialty pharmacists from integrated specialty pharmacies within an Accountable Care Organization and reported saving $1,274 per patient compared to $787 per patient in the present evaluation.[10] These differences in cost avoidance comparing other models can likely be explained by differences in the medications monitored by the CSMM clinic and the medication pricing specific to the VA system.[9,12] For example, a large proportion of patients seen by the CSMM clinic in this evaluation are from rheumatology, dermatology, and cardiology services, whereas Lankford et al focused on oncology. Compared to other evaluations of specialty pharmacist interventions, this clinic is not expected to impact patient out-of-pocket costs given that VA benefits ensure a consistent co-pay for these agents.[6]

Limitations

There were several limitations for this retrospective chart review. First, there were limitations in the amounts used to estimate cost avoidance. This evaluation is likely a conservative estimate of the cost avoidance ROI as it only focuses on interventions where a cost could be assigned. There were 6 interventions with the potential for cost avoidance to which we were not able to assign a cost. Additionally, CPPs in the CSMM clinic perform other roles that were not considered interventions for this review, such as screening and coordination for indicated vaccines or ensuring that appropriate hepatitis B, hepatitis C, and tuberculosis labs were performed. Lastly, in the private sector there may be opportunities for appointment reimbursement, which would further improve the cost benefit implications of a similar clinic.

There were also several key assumptions related to cost, specifically when evaluating disease state control. It was assumed that no medication intervention would have occurred between the time of CPP intervention and the next clinic appointment and assumes patients would have continued to fill their specialty medication regularly. Both assumptions could vary widely in reality and affect the total cost difference. Additionally, no specific cost avoidance data could be found related to disease state control of ankylosing spondylitis. It was assumed the all-cause medical cost would be similar to rheumatoid arthritis and the average monthly cost avoidance for rheumatoid arthritis was used for the one ankylosing spondylitis disease state management intervention.

There were also measurement limitations in this evaluation. There was no comparator group or pre-post analysis, reducing the ability to show the net impact of outcomes directly linked to the CSMM clinic's creation. The time needed to perform the interventions was not collected. Additionally, this is the estimated cost avoidance from a functioning CSMM clinic; it does not take startup time or startup resources into account. Lastly, this data is also limited by being a single site evaluation.

Future Directions

Future directions include expansion to additional specialty medications and disease states as well as expanding data capture to include a comparator group. Additionally, this could be disseminated to other VA hospitals that could benefit from a CSMM strategy. One way to disseminate may be through a hub-and-spoke model for smaller sites that may not have the resources to support a similar clinic where a larger facility is able to offer the CSMM clinic to their patients.[18,19]

Conclusion

A centralized specialty medication management model can result in cost avoidance for patients initiating a specialty medication through pharmacist interventions. Future directions include clinic expansion to additional VA facilities.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

The interim results of this work were presented at the Wisconsin Pharmacy Residency Conference in April 2021.

Acknowledgments: The authors would like to acknowledge Tyler Albright and Samuel Taylor for their assistance with data collection and Anna White for her assistance with the centralized specialty medication management clinic.

Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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Original Work

Impact on Loop Diuretic Doses When Combining with Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure

by Marcus Pribyl, PharmD, Jared Verber, PharmD

Abstract

Objective: The primary objective of this evaluation was to determine loop diuretic doses when establishing patients on sodium-glucose cotransporter-2 inhibitors (SGLT2i) in patients with heart failure with reduced ejection fraction (HFrEF). A secondary objective was to evaluate the correlation between the risk of developing acute kidney injury (AKI) or dehydration leading to emergency department (ED) visits when combing SGLT2i with loop diuretics compared to loop monotherapy.

Methods: This quality improvement project used retrospective observational design. Through chart review, patients were included if they were being followed by the SSM Health Monroe Clinic cardiology clinic with a diagnosis of HFrEF and were using a loop diuretic. Patients were separated into the combination group, which included those who were using both an SGLT2i and a loop diuretic, or the control group if they were utilizing a loop diuretic as monotherapy. Data was collected upon initiation of SGLT2i, at 3 months, at 6 months, at 1 year, and at the end of the evaluation. The dose of loop diuretic normalized to furosemide equivalents was recorded along with the patients' renal labs.

Results: The patients in the combination group had an ~ 8 mg/day reduction in their average loop diuretic usage compared to an increase of about 6 mg/day in the loop monotherapy group. There was no indication of a difference in rates of acute kidney injury between the two groups.

Conclusions: Providers should monitor for the opportunity to reduce loop diuretic doses when initiating an SGLT2i. There were no major changes in renal function when adding an SGLT2i to loop diuretics in patients with HFrEF.

In 2020, heart failure impacted around 6.2 million Americans and in 2018 accounted for 13.4% deaths in the country.[1] Heart failure cost the United States $30.7 billion in 2012, and that number has been expected to rise even more with the increased cost of healthcare and medications.[2] Currently, the American Heart Association and American College of Cardiology recommend a multifaceted approach to treating heart failure with reduced ejection fraction.[3] This includes but is not limited to angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNI), beta blockers, aldosterone antagonists, diuretics, and other individualized therapies. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce major cardiac events (MACE) and were added as one of the pillars of guideline-directed medical therapy for heart failure, regardless of type II diabetes status, due to removal of more fluid and sodium to reduce strain on the heart.[3] The American Diabetes Association (ADA) also recommends using SGLT2i in diabetes patients if they have heart failure or have a history of cardiovascular disease or chronic kidney disease.[4]

The combination of a loop diuretic and SGLT2i can result in increased diuresis.[3] This is due to the loop diuretic's ability to block sodium and chloride reabsorption in the loop of Henle, causing water to follow the higher salt content into the concentrated urine. Since SGLT2is work in the proximal tubule before the loop of Henle, this results in additional diuresis before the loop diuretic takes effect downstream. This additive effect could be beneficial in managing heart failure patients' fluid levels. However, in theory this can also lead to dehydration, acute kidney injury (AKI) and long-term kidney damage if not managed properly. This could put heart failure patients with fragile renal function at risk for further damage if these medications are not properly managed.

Currently, there is limited information available regarding the use of loop diuretics with SGLT2i. Heise and colleagues conducted a crossover study that compared the effects on serum creatinine (Scr) among 22 patients using empagliflozin and torsemide, compared to using one of the agents individually.[5] Patients were given one agent (either empagliflozin or torsemide) for a period of 5 days. Patients then went through a washout period and were given the other agent individually or both agents for 5 days, followed by a 5-day washout period, and then received the final 5-day treatment of the group they had not received yet. Scr levels were evaluated after each period. Over this time, patients undergoing therapy with both empagliflozin and torsemide had a Scr increase of 0.7 mg/dL ($p<0.05$) compared to either agent individually. This indicates that upon initiation of these agents there is potential

for renal damage and AKI.

Charaya and colleagues looked at patients admitted to the hospital for acute heart failure exacerbation and compared 50 patients receiving dapagliflozin 10 mg to 52 patients receiving placebo.[6] All patients received standard of care medications during their hospital stay, which included loop diuretics. Patients who were already initiated on a loop diuretic were also included in this trial. The primary outcome of renal function decline (defined as a Scr increase of 0.3 mg/dL or greater in less than 48 hours) found a prevalence rate of 34.4% of patients in the dapagliflozin group compared to 15.2% in the placebo group but was not statistically significant (p=0.07). It was also found that loop diuretic doses were an average of 78 mg/day in the treatment group compared to 102 mg/day in the placebo group (p=0.001).

Wilcox and colleagues evaluated the effects on Scr when using bumetanide and dapagliflozin in 42 patients.[7] Patients were randomized to receive one week of either dapagliflozin 10 mg, bumetanide 1 mg, or both. Then after one week, they received the combination of dapagliflozin 10 mg and bumetanide 1 mg for one week. In all groups they found a 0.1 mg/dL increase in Scr after 8 days of therapy (p<0.005). This study indicates the two medication classes might not have a clinically significant medication interaction.

Recently, the EMPEROR-Preserved Trial completed a post hoc analysis in 5,815 patients who were using loop diuretics with empagliflozin who had heart failure with preserved ejection fraction.[8] Patients were taking either empagliflozin or placebo and receiving loop diuretics dosed to their fluid status. It was found that patients who were taking empagliflozin were found to have a decreased chance of loop diuretic dose escalation compared to placebo (HR, 0.74; 95% CI, 0.65-0.84). It was also found that patients who were taking empagliflozin were more likely to require a loop diuretic dose reduction (HR, 1.15; 95% CI, 1.02-1.30). The empagliflozin group was also associated with an increased risk of volume depletion compared to placebo (HR, 1.34; 95% CI, 1.13-1.59). This study highlights the possible risk when combining these two medication classes in HFpEF but does not address patients diagnosed with HFrEF..

These studies are limited by short duration or small patient populations, or did not discuss patients with HFrEF. Even with these limitations, the studies do illustrate the potential for renal damage with the combination therapy, which warrants further investigation. The objective of this evaluation was to determine loop diuretic doses when patients with HFrEF were initiated on an SGLT2i.

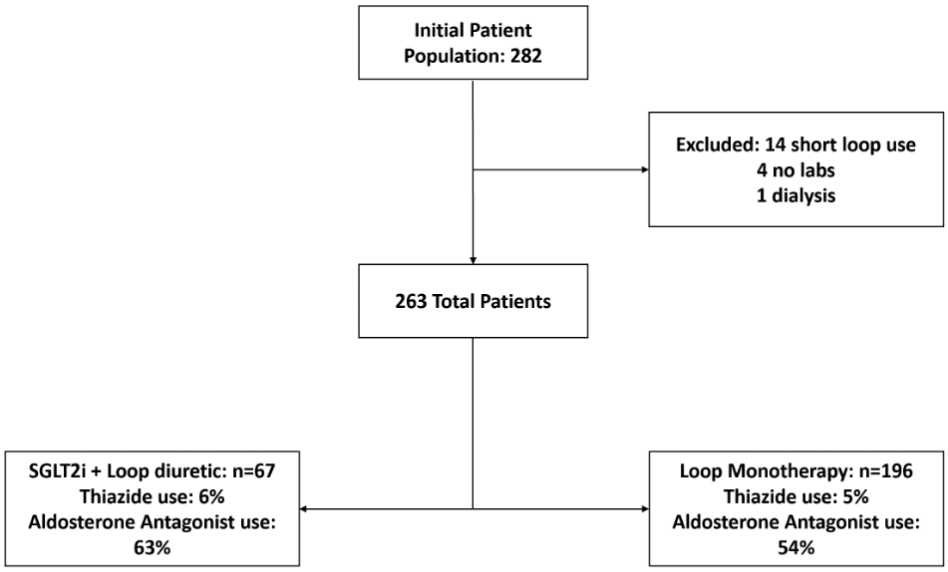
Methods

The SSM Health Monroe Clinic's cardiology clinic sees a variety of patients for cardiology related disease states including, but not limited to, heart failure, hypertension, coronary artery disease, and various arrythmias. Patients can self-refer or be referred by another provider to be seen in the clinic. The cardiology clinic employs an ambulatory care pharmacist who sees patients with a cardiologist for one half-day day per week for patients with a diagnosis of heart failure, regardless of classification. These cardiology clinic visits focus mostly on the respective disease state for which the patient was referred. Patients are typically seen in 3-month intervals initially with follow-ups lengthening as greater control of the disease state is achieved.

To identify patients for this retrospective evaluation, the electronic medical record's search function was used to perform a patient search to identify patients who received care at the Monroe Clinic Cardiology Clinic with a diagnosis code for HFrEF and who had been taking a loop diuretic since 2018. The patient list ran through June 2022 when the search was completed. Patients were included in the evaluation if they had a diagnosis of HFrEF and were taking a loop diuretic and/or an SGLT2i. The combination group was considered to be patients who were taking both an SGLT2i and a loop diuretic and the control group was defined as the patients who were only taking a loop diuretic. All SGLT2i medications at any dose were included in this evaluation, independent of target HFrEF dose and prescribed indication. Patients were excluded from this evaluation if they had only used a loop diuretic for less than 1 month, no lab data was available, or they were receiving dialysis. Data were collected via chart review at the following time points: baseline initiation of SGLT2i, 3 months, 6 months, 1 year, and end of evaluation (June 2022). At each time interval, the patient's daily loop diuretic dose was recorded and converted to furosemide equivalents. Renal labs (Scr, blood urea nitrogen [BUN]) and any emergency department (ED) visits with a primary diagnosis of AKI or dehydration were also collected at each time interval. Use of a thiazide diuretic or an aldosterone antagonist were recorded as possible confounding variables.

The primary outcome for this evaluation was the reduction of loop diuretic doses after initiation of an SGLT2i. Secondary outcomes included number of ED visits due to AKI or dehydration along with

FIGURE 1. Patient Inclusion Into Evaluation



changes in renal labs (Scr and BUN). Once all patient data was collected, the mean daily loop diuretic dose (in furosemide equivalents) in each group was calculated along with mean Scr and BUN at each time interval. A two-sample t-test was used to determine statistical significance between the two groups for mean daily loop diuretic use. Some patients were taking a loop diuretic on an as-needed basis at various points during the review. This data was important to capture because it still represents a dose change. To try to capture the true value of a patient's loop diuretic usage, the mean loop diuretic dose was calculated under the assumption that the as-needed dose was 0 mg per day initially. Then a sensitivity analysis was completed assuming the loop diuretic usage was 20 mg of furosemide per day because this is what the as-needed patients were prescribed.

Results

When the initial data pull was completed, 282 patients were identified as candidates for this evaluation. After completing chart reviews of patients, 19 were excluded due to at least one of the following reasons: short term course of a loop diuretic (defined as less than 1 month of therapy), no labs were available for the patient, or patient was on dialysis. Of the remaining 263 patients, 67 were taking an SGLT2i. The loop diuretic monotherapy group was comprised of 196 patients (Figure 1). Regarding concurrent diuretic use, similar proportions of patients used thiazides in the combination group compared to the loop diuretic monotherapy group (6% vs. 5%, respectively). A higher proportion of patients took aldosterone antagonists in the combination group compared to the loop diuretic monotherapy group (63% vs. 54% respectively).

Some patients used a loop diuretic only as needed in both groups. This value varied throughout the evaluation timeline as some patients transitioned on and off an as-needed dose (Table 1). Table 2 indicates the mean loop diuretic dose (in furosemide equivalents) if the patients were taking 0 mg per day of their furosemide, and Table 3 indicates the mean dose if they were taking 20 mg per day of furosemide. For patients who were taking SGLT2is, the mean loop diuretic dose at baseline was 53.1 ± 0.4 mg of furosemide per day compared to 45.0 ± 0.2 mg per day in the monotherapy group. Following combination therapy, the average loop diuretic dose decreased to 46.9 ± 0.6 mg and 45.2 ± 0.8 mg after 6 months and 1 year, respectively. The mean loop diuretic dose in the monotherapy group increased to 47.1 ± 0.2 mg at 6 months and 48.4 ± 0.3 mg at 1 year (Tables 2 and 3). See Table 4 for mean changes in daily loop diuretic dose.

For patients who were taking both an SGLT2i and a loop diuretic, the average baseline Scr was 1.19 mg/dL and the average BUN at baseline was 24.76 mg/dL. Patients who were taking only a loop diuretic had an average baseline Scr of 1.17 mg/dL and BUN of 25.17 mg/dL. After 6 months of therapy the loop monotherapy group increased to 110% of the original Scr baseline level, compared to the combination group staying at 106% of the original Scr baseline level (Table 5).

TABLE 1. Number of patients on a PRN Loop Diuretic

Number of Patients	*Baseline*	*3 Months*	*6 Months*	*1 Year*	*End of Evaluation*
Loop Monotherapy	5	4	4	4	2
SGLT2i + Loop Diuretic	3	7	5	3	2
PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors					

TABLE 2. Mean Daily Loop Diuretic Usage (prn = 0 mg/day)

(Doses Adjusted to Furosemide Equivalents)	*Baseline (mg/day)*	*3 Months (mg/day)*	*6 Months (mg/day)*	*1 Year (mg/day)*	*End of Evaluation (mg/day)*	*P-value (baseline to end of Evaluation)*
Loop Monotherapy	44.8	47.5	46.9	48.2	51.2	0.104
SGLT2i + Loop Diuretic	52.7	50.6	46.3	44.4	44.0	0.302
PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors						

TABLE 3. Daily Loop Diuretic Usage (prn = 20 mg/day)

(Doses Adjusted to Furosemide Equivalents)	*Baseline (mg/day)*	*3 Months (mg/day)*	*6 Months (mg/day)*	*1 Year (mg/day)*	*End of Evaluation (mg/day)*	*P-value (baseline to end of Evaluation)*
Loop Monotherapy	45.2	47.9	47.3	48.7	51.6	0.103
SGLT2i + Loop Diuretic	53.4	52.3	47.5	46.0	45.6	0.346
PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors						

TABLE 4. Average Change in Loop Diuretic Usage

	PRN = 0 mg/day	*PRN = 20 mg/day*
Loop Monotherapy	6.3 mg/day	6.4 mg/day
Loop + SGLT2i	-8.8 mg/day	-7.8 mg/day
P values	p=0.049	p=0.06
PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors		

The breakdown of the number of patients who were taking each SGLT2i is listed in Table 6. The two patients who were prescribed canagliflozin were initially prescribed empagliflozin but were changed due to insurance coverage. The most common SGLT2i used was empagliflozin (75%).

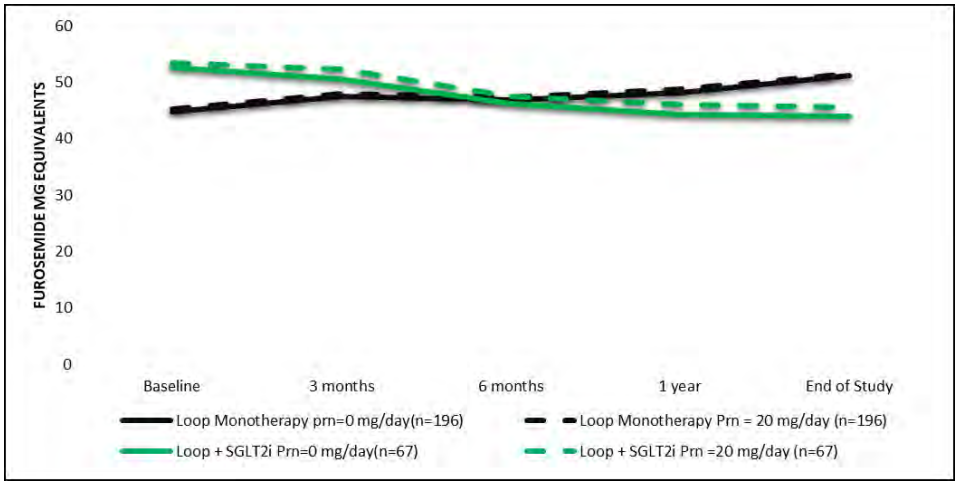
The proportion of patients who presented to the ED with a primary diagnosis of dehydration or AKI was 3% for patients in the combination group and 2.6% for the loop monotherapy group. The 2 patients who presented to the ED in the combination group were both on empagliflozin 10 mg daily.

Discussion

We found that loop diuretic doses were reduced by about 8 mg/day in the combination group compared to a dose increase of about 6 mg/day in the monotherapy group over time. There was no clinically significant change in Scr when comparing the two groups, and based on Table 5, the combination group may have demonstrated a slower rate of renal decline. The slight increase in BUN for the combination group was likely due to a higher amount of fluid loss if patients were possibly less hydrated compared to the monotherapy group. However, this risk was not shown in the proportion of ED visits due to dehydration or AKI, with clinically insignificant differences between the two groups.

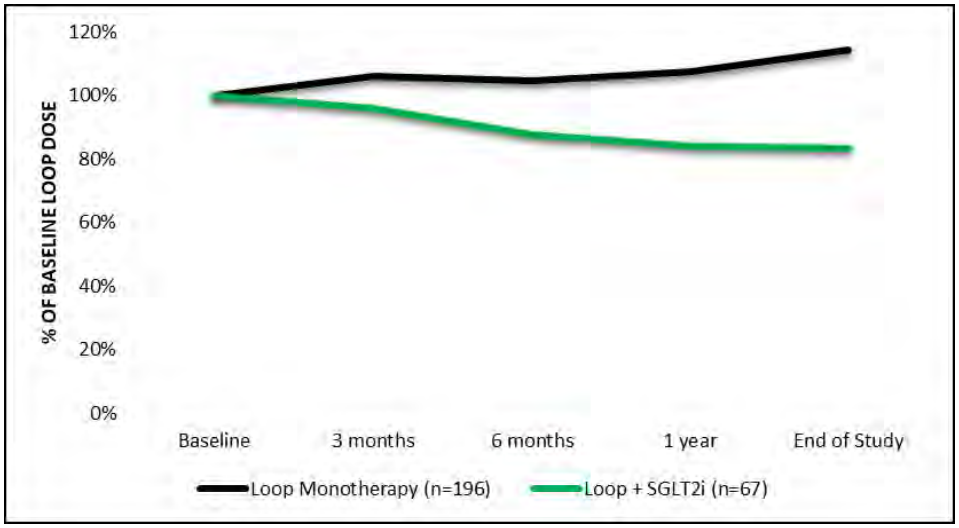
It was noted that patients in the combination group had a higher loop diuretic dose prescribed at baseline compared to the loop monotherapy group. One potential explanation for this is the cost of SGLT2is compared to loop diuretics. With SGLT2is being a more expensive medication, patients may be less willing to initiate an SGLT2i early on with a less advanced disease. However, patients may be more willing to try a more expensive agent for increased fluid output if their heart failure progresses and continues to worsen. The SGLT2i class is considered first-line agents for management of heart failure and are recommended to be initiated when a patient is diagnosed, which is not always seen in practice.[3] These agents are also recommended for patients with type 2 diabetes if patients also have a diagnosis of heart failure, cardiovascular disease, or chronic kidney disease.[4]

FIGURE 2. Loop Diuretic Dose Over Time



PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors

FIGURE 3. Percent of Loop Dose From Baseline



PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors

This evaluation does indicate that there is likely a pharmacodynamic interaction of increased diuresis that should be monitored when using an SGLT2i with loop diuretics. The rates of thiazide diuretics and aldosterone antagonists were relatively similar between the two groups, indicating these are unlikely to have a major impact on the results. Compared to the current literature, this evaluation closely examined the long-term concomitant use of SGLT2i and loop diuretics in patients with HFrEF.[5-7] Current literature is limited to studies with short duration or patients with HFpEF.[8] Furthermore, our findings mitigate the potential concern for renal damage in patients who have HFrEF on combination loop diuretic and SGLT2i who tend to be a more vulnerable population.

It may be reasonable in some circumstances to empirically reduce a patient's loop diuretic dose by 10 mg/day of furosemide. One circumstance where it would be reasonable to empirically reduce a patient's loop diuretic is if they have well controlled heart failure and are interested in starting an SGLT2i. In this situation the increased diuresis from the SGLT2i would likely require a dose reduction in the future due to being euvolemic. However, more data is needed to make a strong empiric dose reduction recommendation.

This evaluation is not without limitations and those should be noted. One limitation was the inability to quantify how often patients were taking their loop diuretic when they were using it as needed.

To try to mitigate this limitation, multiple calculations were performed with different dose assumptions. In addition, adherence rates to SGLT2is and loop diuretics were not tracked. Another limitation was the small number of patients in each group. Some patients could have been taking combination therapy for a longer period of time at the end of the evaluation which could also impact results. With this being a retrospective observational evaluation, there was no control over the prescribing patterns; this evaluation reflects real world practice.

Since there was a statistically significant dose reduction found, it is likely there is some pharmacodynamic interaction that takes place between these two classes of medications. However, further research needs to be completed to discover how strong the interaction is between these two medication classes. One future direction for this topic would be to expand this to other healthcare systems to evaluate if this is something that is observed everywhere or just in a subset of the population.

Conclusion

There was a significant decrease in the loop diuretic dose with combination therapy with no clinically significant impact on renal function when adding SGLT2is to loop diuretics in patients with HFrEF. Based on this evaluation, providers should monitor for the opportunity to reduce loop diuretic doses when initiating an SGLT2i in patients with HFrEF.

TABLE 5. Renal Labs Over Time

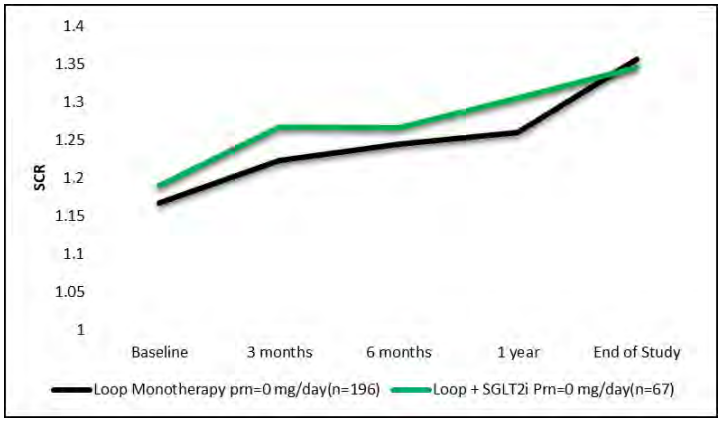
Number of Patients	*Baseline*	*3 Months*	*6 Months*	*1 Year*	*End of Evaluation*
Scr (mg/dL)					
Loop Monotherapy	1.17	1.22	1.24	1.26	1.54
SGLT2i + Loop Diuretic	1.19	1.27	1.27	1.30	1.35
Percent of Baseline Scr					
Loop Monotherapy	-	106%	110%	112%	127%
SGLT2i + Loop Diuretic	-	106%	106%	108%	113%
BUN (mg/dL)					
Loop Monotherapy	25.17	26.15	26.06	27.16	27.06
SGLT2i + Loop Diuretic	24.73	27.59	25.96	27.5	28.83

BUN = blood urea nitrogen; Scr = serum creatinine; SGLT2i = sodium-glucose cotransporter-2 inhibitors

TABLE 6. Prescribing Pattern of Sodium Glucose Cotransporter 2 Inhibitors

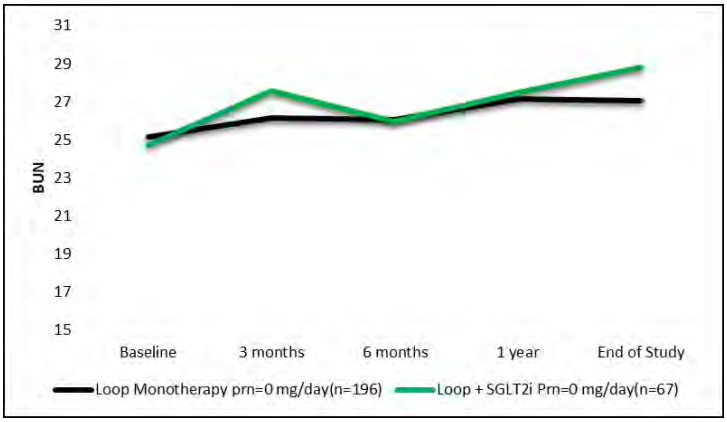
Unique Medications and doses	*Usage rate N (%)*
Dapagliflozin 5 mg	3 (4.5%)
Dapagliflozin 10 mg	11 (16.4%)
Canagliflozin 100 mg	1 (1.5%)
Canagliflozin 300 mg	1 (1.5%)
Empagliflozin 5 mg	1 (1.5%)
Empagliflozin 10 mg	41 (61.2%)
Empagliflozin 25 mg	9 (13.4%)

FIGURE 4. Serum Creatinine Over Time



SGLT2i = sodium-glucose cotransporter-2 inhibitors

FIGURE 5. BUN Over Time



BUN = blood urea nitrogen; SGLT2i = sodium-glucose cotransporter-2 inhibitors

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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Original Work

A Study of Routine Pharmacogenomic Testing in the Midwest Region: The Current State and Barriers Faced by the Field

by Kelsie E. Tingle, 2025 PharmD Candidate, Paul R. Hutson, PharmD, MS, Emili J. Leary, PharmD

Abstract

Objective: The purpose of this study was to survey major medical facilities in Wisconsin and nearby states about their typical use of pharmacogenomic testing in clinical practice.

Methods: Twenty healthcare systems in Wisconsin and the surrounding region were sent a questionnaire regarding which facilities were and were not implementing pharmacogenomics, along with which genes have been prioritized by those facilities that reported ongoing pharmacogenomic testing.

Results: Fourteen medical centers responded to the survey, and 10 facilities reported testing. Among the respondents, no two facilities tested for the same set of genes. Additionally, no single gene was tested for by all responding facilities.

Conclusions: Pharmacogenomic testing faces several barriers, which include evidence for clinical utility, cost effectiveness, and physician education and awareness. The lack of standardization across facilities implementing pharmacogenomics may be indicative of barriers faced by the field and institution-specific factors; the lack of standardization creates difficulties in comparing data between facilities due to inconsistencies in approach and in genes tested. Pharmacogenomics has the potential to lead to greater medication safety and efficacy, but its expansion would be aided significantly by additional clinician education and appropriate advocacy for the merits of pharmacogenomic testing, both in those facilities currently implementing and those seeking to do so.

Pharmacokinetics is an area of science that analyzes the impact of the body on a given drug over time, including absorption, distribution, metabolism and excretion. Pharmacodynamics, conversely, describes the effects of the drug on the body. As both of these processes are governed by complex processes including enzymes, transporters and receptors, genetic variation has the potential to result in significant differences in patient response to identical dosing regimens. A growing understanding of the relationships between gene and drug action or elimination is leading to the expansion of interest in incorporating pharmacogenomics into clinical practice. Pharmacogenomics is centered around the relationship between an individual's genes and their predicted response to a particular drug. Considering the variation between patients' genetic profiles allows for a personalized prediction of how those patients may differ in their response to a particular treatment given current evidence.

Clinicians must consider a wide variety of factors when determining the best medication and dosing for a given patient. These factors include age, lifestyle, disease states, allergies, and other medications. Based upon clinical judgement, a dose is then selected from a range of Food and Drug Administration (FDA) approved dosing for a given indication, which was determined by the design of pre-market clinical trials involving the response of a large pool of patients. Rather, the doses and regimens included in FDA approved labelling of the drug identify doses that are tolerable and effective for the majority of individuals, usually without consideration of an individual patient's pharmacogenomic profile. When used properly, pharmacogenomics provides an additional measure of safety and efficacy in its ability to individualize the treatment and potentially avoid a significant drug-gene interaction that would warrant a deviation from standard dosing and medication selection. This additional information decreases the chance that the patient will experience toxicities or therapeutic failure with their dosing regimen, allowing for improvements to safety, efficacy and optimal dosing.[1]

Pharmacogenomic testing typically follows one of two models: reactive or preemptive. Preemptive testing aims to obtain the genetic information necessary to determine pharmacogenomics-guided medication dosing in advance of the initiation of drug therapy. Reactive testing, conversely, typically occurs following an adverse drug reaction or a lack of therapeutic response as a method of identifying possible genetic causes for the unfavorable response to the drug regimen. To maximize the potential of preemptive testing, the patient's pharmacogenes are evaluated across many genes, providing information regarding numerous genetic variants, and the resulting data is stored using an electronic health record (EHR) for immediate as well as future application.

Ideally, these results would be used with clinical decision support (CDS) to generate alerts and suggested changes to the drug regimen when relevant interactions are identified.[2]

Several organizations have been founded to study and promote the incorporation of pharmacogenomics testing results into clinical decision-making. These include the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenomics Working Group, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), the French National Network of Pharmacogenetics (RNPGx) and the Pharmacogenomics Knowledgebase PharmGKB. PharmGKB is a National Institutes of Health (NIH)-funded resource that collects, curates and disseminates information about clinically actionable gene-drug associations.

Several innovative United States (US) institutions such as St. Jude Children's Research Hospital routinely obtain preemptive pharmacogenomics tests on children treated at their facility.[3] The Veterans Affairs Pharmacogenomic Testing for Veterans (PHASER) program provides free pharmacogenomics testing at participating Veterans Affairs (VA) medical centers, with additional sites being added.[4] The Ubiquitous Pharmacogenomics (U-PGx) consortium has implemented routine, pre-emptive pharmacogenomic testing in multiple countries in the European Union.[5] The NIH National Human Genome Research Institute supports clinical trials within the Implementing Genomics in Practice (IGNITE) Pragmatic Clinical Trials Network to develop clinical trials to establish clinical decision support tools to guide drug treatment adjustments.[6] Despite the growth and productivity of these collaborative efforts, implementation of routine pharmacogenomic testing in the US is not yet the standard of care. An important step towards incorporating pharmacogenomics as the standard of care is evaluation of the current landscape and status of pharmacogenomics testing. The purpose of this study was to survey major medical facilities in Wisconsin and nearby states about their use of pharmacogenomic testing in clinical practice, including which genes are tested by each facility.

TABLE 1. Examples of Genes with CPIC Guidelines

Gene	*Gene Function*	*Examples of Common Drugs Associated with Each Gene*	*Examples of Effects Related to Genotype*
CFTR	Drug Target Protein	Ivacaftor	Certain genetic variations of *CFTR* may prevent effective treatment by Ivacaftor by interfering with the drug's mechanism.
CYP2B6	Metabolism Enzyme	Efavirenz	Impaired *CYP2B6* function may increase the risk for CNS-related toxicities and discontinuation of treatment.
CYP2C9	Metabolism Enzyme	Phenytoin	Decreased function of *CYP2C9* can lead to higher plasma concentrations that contribute to increased risk of toxicities.
		Ibuprofen and other NSAIDS	Reduced function of *CYP2C9* may result in higher plasma concentrations which may increase the risk and severity of toxicities
CYP2C19	Metabolism Enzyme	Clopidogrel	Decreased function of *CYP2C19* can lead to suboptimal clopidogrel response and lead to higher risk of major adverse cardiovascular and cerebrovascular events compared to treatment with other antiplatelet therapies.
		Citalopram and other SSRIs	Impaired *CYP2C19* function can result in higher plasma concentrations which may increase the probability of side effects.
CYP2D6	Metabolism Enzyme	Codeine	Increased *CYP2D6* function can lead to increased formation of morphine, resulting in a greater risk of toxicity. Reduced *CYP2D6* activity can lead to decreased morphine formation and diminished analgesia.
		Paroxetine and other SSRIs	Impaired *CYP2D6* function can result in higher plasma concentrations which may increase the probability of side effects.
		Ondansetron	Increased *CYP2D6* function can lead to increased metabolism, associated with decreased efficacy.
DPYD	Metabolism Enzyme	Capecitabine Fluorouracil	Reduced *DPYD* function can lead to increased risk for severe/potentially fatal drug toxicity with fluoropyrimidine drugs.
G6PD	Toxicity Mediator Enzyme	Rasburicase	*G6PD*-deficiency results in a greater risk for acute hemolytic anemia.
HLA-A	Immune System Recognition Protein	Carbamazepine	The HLA-A*31:01 positive genotype results in a greater risk of carbamazepine-induced Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis, as well as drug reaction with eosinophilia and systemic symptoms or massive pulmonary embolism.
HLA-B	Immune System Recognition Protein	Carbamazepine Phenytoin Oxcarbazepine	The HLA-B*15.02 positive phenotype results in an increased risk for drug-induced Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis.
		Allopurinol	The HLA-B*58:01 phenotype significantly increases the risk of allopurinol-induced severe cutaneous adverse reactions.
		Abacavir	The HLA-B*57:01 phenotype results in a significantly increased risk of abacavir hypersensitivity.

Methods

Twenty healthcare systems in Wisconsin and neighboring states were sent a questionnaire in the spring of 2022. In some cases, the survey was forwarded from the original contact to a different individual for completion. The survey asked which facilities were and were not implementing pharmacogenomic testing, along with which genes were tested. The survey questioned facilities about 14 genes, each of which has clinically actionable guidelines provided by CPIC (Table 1). The list of genes of pharmacogenomic interest considered in this study was not exhaustive, but rather consisted of genes with strong evidence to support prescribing decisions based upon genetic information. In total, 14 genes and the drug pairs they are associated with were displayed alongside examples of genotype-associated risks reported in CPIC guidelines.[7–21] The information reported by the surveyed facilities was compared and displayed. Facilities were additionally given the opportunity to disclose additional genes offered in their pharmacogenomic testing panels. A reminder email was sent with a link to the survey to institutions that did not respond to the initial request. Institutional Review Board exemption was obtained from the University of Wisconsin-Madison.

TABLE 1. Examples of Genes with CPIC Guidelines - Continued

Gene	*Gene Function*	*Examples of Common Drugs Associated with Each Gene*	*Examples of Effects Related to Genotype*
IFNL3/ IFNL4	Unclear Mechanism	Ribavirin	Individuals carrying the unfavorable response allele, or the T allele, have a decreased likelihood of response, or a lower systemic vascular resistance rate to therapy with ribavirin.
		Peginterferon alfa-2a	Individuals carrying the unfavorable response allele, or the T allele, have a decreased likelihood of response, or a lower systemic vascular resistance rate to therapy with peginterferon alfa-2a.
NUDT15	Metabolism Enzyme	Azathioprine Mercaptopurine	A decrease in function of NUDT15 increases the risk of thiopurine-related leukopenia, neutropenia and myelosuppression.
SLCO1B1	Transporter Protein	Atorvastatin Simvastatin	Decreased SLCO1B1 function may lead to increased risk of myopathy due to increased atorvastatin and simvastatin exposure.
TPMT	Metabolism Enzyme	Azathioprine Mercaptopurine Thioguanine	Decreased TPMT function may lead to high concentrations of TGN metabolites, contributing to toxicity which may lead to leukopenia, neutropenia, myelosuppression, or death.
UGT1A1	Metabolism Enzyme	Irinotecan	Impaired function of UGT1A1 may lead to a greater probability of toxicity.

CPIC = Clinical Pharmacogenetics Implementation Consortium; CNS = central nervous system; NSAID = non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor

TABLE 2. Tested Pharmacogenomic Genes of Interest Reported by Surveyed Facilities

Facility	Children's Wisconsin	Mayo Clinic	St. Jude Children's Research Hospital	University of Illinois Hospital	William S. Middleton Memorial Veterans Hosptal	Children's Minnesota	Gundersen Health System	Marshfield Clinic Health Systems	Indiana University School of Medicine	Michigan Medicine
CYP2D6		✓	✓		✓	✓		✓	✓	
CYP2C19		✓	✓	✓	✓	✓		✓	✓	✓
CYP2C9		✓	✓	✓	✓	✓		✓		✓
CYP2B6			✓			✓		✓		
TPMT	✓	✓	✓		✓	✓	✓	✓	✓	✓
DPYD		✓	✓		✓	✓	✓	✓	✓	✓
UGT1A1		✓	✓			✓	✓	✓	✓	✓
NUDT15	✓	✓	✓			✓	✓	✓	✓	
HLA-B		✓				✓		✓	✓	✓
HLA-A		✓				✓		✓		
SLC01B1		✓	✓		✓	✓		✓	✓	
CFTR	✓					✓			✓	
G6PD			✓			✓	✓		✓	✓
IFNL3/IFNL4					✓	✓			✓	

Results

Fourteen of the 20 medical centers contacted for this survey responded. Of the 14 healthcare systems responding, seven were institutional facilities affiliated with Big Ten universities, while the other seven participants were regional health systems and hospitals. Four facilities reported that pharmacogenomic testing was not incorporated into their patient care process. The responses from the remaining 10 facilities can be seen in Table 2. Notably, only one of these 10 facilities reported pharmacogenomic testing for all 14 genes included in the survey. No two facilities were observed to test for the same panel of genes when considering the additional genes reported by facilities (Table 3).

It is notable that no one gene was tested by every responding facility. Nine facilities reported testing for *TPMT* for patients receiving thiopurines, eight facilities reported testing for *CYP2C19*, and a different set of eight facilities reported testing for *DPYD* for patients receiving 5-fluorouracil. Genes that were less commonly reported included *HLA-A*, which was only tested for at three of the responding facilities. *IFNL3/IFNL4*, *CFTR* and *CYP2B6* were only reported by four facilities each.

Discussion

Despite the routine use of pre-emptive pharmacogenomic testing in many United States VA medical centers[4], and in some European countries, pre-emptive testing is not commonly or consistently employed, as was observed in our survey results. Commonly cited barriers to pharmacogenomic implementation include lack of evidence for clinical utility, lack of evidence for cost effectiveness, and lack of physician education and awareness.[22] Clinical utility of pharmacogenomic testing has been questioned due to a lack of randomized controlled trials (RCTs), which are generally considered the gold standard for considering new interventions or tests. Legitimate concerns exist about the use of RCTs in evaluating pharmacogenomics, as randomizing patients who carry known and actionable pharmacogenomic variants to treatments known to be suboptimal or even harmful would be unethical.[23]

Cost-effectiveness evaluations of pharmacogenomics are influenced by a wide variety of factors including the site at which testing occurs (e.g., institutional billing model considerations, specialty focus, etc.), whether the test is performed by a commercial vendor or on-site at the facility (e.g., consideration of patient assistance programs, platform used, etc.), and whose perspective is being evaluated in the cost-effectiveness evaluation (e.g., societal, health system, payer or patient perspectives). Cost effectiveness evaluations are further complicated by widely variable reimbursement (e.g., federal vs commercial insurers and associated caveats). There is not currently widespread insurance coverage for pharmacogenomic testing. When full or partial reimbursement is available, however, it can play a significant role in the decision to pursue pharmacogenomic testing, influencing both the physician and the patient.[22] A significant difference is observed in the accessibility of germline and somatic pharmacogenomic testing due to lack of coverage for germline variants. In contrast to the reimbursement struggles faced by germline pharmacogenomic testing, tumor/biopsy testing for actionable somatic mutations is more likely to be covered by medical insurance.[24]

A lack of physician education presents another significant challenge to overcome in clinical implementation of pharmacogenomic testing; it is generally the physician who advocates for the testing and is responsible for ordering the test for the patient at implementing facilities as pharmacists often do not have the authority to order testing without a collaborative practice agreement (CPA) in place. Without advanced training in pharmacogenomic testing including test benefits, risks and limitations, it may be challenging for physicians to utilize pharmacogenomic testing appropriately and to its full potential. The lack of trained and/or experienced personnel in pharmacogenomics may explain why many facilities are hesitant to initiate or expand pharmacogenomic testing. In a 2012 survey of physicians that were board-certified in family or internal medicine, Haga et. al. found that 306 of 597 respondents, or more than half of those surveyed, felt they were not properly informed about how to

TABLE 3. Additional Pharmacogenomic Genes of Interest Reported by Surveyed Facilities

Facility	Children's Wisconsin	Mayo Clinic	St. Jude Children's Research Hospital	University of Illinois Hospital	William S. Middleton Memorial Veterans Hospital	Children's Minnesota	Gundersen Health System	Marshfield Clinic Health Systems	Indiana University School of Medicine	Michigan Medicine
Additional Genes Reported		NAT2, CYP3A4, CYP3A5, CYP1A2, VKORC1, CYP4F2, CYP2C cluster (rs12777823), HTR2A, HTR2C, COMT, DRD2, CHRNA3, EPHX1, GRIK4, OPRM1, SCN1A, UGT2B15, ANKK1, ADRA2A, SLC6A4, MT-RNR1	mt-RNR1, CACNA1S, RYR1, CYP3A5		CYP2C, CYP3A5, CYP4F2, VKORC1	RYR1/CACNA1S-MHS, CYP3A5 - Tacrolimus, CEP72-VIPN (research), CYP4F2/VKORC1 (not using clinically at this time), F2, F5		CYP3A4, CYP4F2, F2, F5, VKORC1		

interpret pharmacogenomic test results. Another 131 respondents denied receiving any education on the subject, and 435, or almost three quarters of the physicians, did not feel qualified to use pharmacogenomic tests or to interpret the results.[22,25] A more recent survey of physicians conducted by Smith et. al. in 2020 had similar findings, noting that only 26% of physicians surveyed felt confident using pharmacogenomic results for clinical decision-making. The same study also found that 70% of providers wanted a pharmacist consultation for help interpreting pharmacogenomic results.[26]

Another factor that may influence a facility's ability to expand their testing is the laboratory with whom they contract for testing. Facilities that test in-house may have more flexibility in which genes/genotypes they choose to test for, depending upon the platform and technology they utilize. Whole genome sequencing (WGS) is not the standardized method for pharmacogenomic testing at this time due to upfront cost as well as data processing and storage concerns, so most pharmacogenomic testing only queries variants that have been identified and specifically screened for (e.g., genotyping). Other variants that are not known or specifically assessed will be missed, leading to incorrect categorization of genes as "wild-type" in the reported results, regardless of whether their impact on metabolism matches that of the wild-type state.[27] Thus, if a vendor does not test for certain low frequency variants in a particular gene, the reported results may incorrectly indicate a normal, wild-type genotype.[28] Similarly, the genes each facility reported testing for may reflect the genes routinely tested by their third-party vendor. The vendor selection may be influenced by factors including (but not limited to) the primary indication for testing, patient cost, institutional contract pricing, gene offerings and coverage of genes labeled actionable by CPIC and the FDA, and integration of results into the medical record, with or without Clinical Decision Support (CDS) interface.

Limitations of this study exist, in addition to those inherent in survey research (e.g., biased nature of solicited responses and targeted demographic, etc.). Although several institutions affiliated with the Big 10 Academic Alliance along with select other healthcare systems across the state of Wisconsin were included in this survey, the list was not inclusive. Additionally, not all facilities had a clear point of contact listed for pharmacogenomic testing; thus, it was difficult to identify the most appropriate individual to receive the current survey for each facility; at times the survey was forwarded from the original recipient to another individual within the organization to complete the survey. This lack of clarity in identifying the most relevant expert in pharmacogenomics for a facility reflects the growing nature of the field, as pharmacogenomic testing is not yet prevalent or consistently applied. This may have impacted the generalizability of the results, as the data presented is only as accurate as the data that was reported through the questionnaire; notably, this also speaks to the need for more experts in the field.

Conclusion

Pharmacogenomic testing has been recognized as a useful tool to improve drug regimens in some clinical centers. Just as genetic testing of biopsied tumors is used to identify the somatic mutations associated with cancers to help optimize treatment, germline pharmacogenomic testing can be used to avoid potentially harmful treatments and, in some cases, optimize dosing. We found that pharmacogenomic testing is not standardized across different facilities in Wisconsin's region: some health care systems are implementing pharmacogenomic testing to varying extents, with others not yet implementing it at all. Improved sharing of best practices to identify and overcome barriers by facilities will be important in expanding routine pharmacogenomic testing, and it might encourage other facilities to begin implementing routine pharmacogenomic testing.

When considering the lack of standardization across facilities, two possibilities arise for future consideration. First, the lack of consistency in genes may be representative of different barriers faced by different healthcare systems, as well as institution-specific factors like the primary demographic served by that institution (e.g., institutions that focus on cancer may focus testing on genes more pertinent for oncology, namely *DPYD* and *TPMT*, versus another institution that focuses more on genes like *CYP2C19* and *SLCO1B1* for cardiology). Another possibility is that the lack of standardization itself may be a barrier to further implementation by making it difficult to track health outcomes of pharmacogenomic testing across different facilities. Next steps in advancing pharmacogenomic testing throughout the region may include evaluating the barriers to engaging in pharmacogenomic testing and directly querying which factors impacted selection of genes for each surveyed facility, as well as obtaining improved cost-utility data from the EHRs of participating facilities.

It is also vital to further clinician education in the area of pharmacogenomics by expanding the precision medication and genetics education provided in both medical and pharmacy schools, as well as offering and promoting more continuing education opportunities in the area of pharmacogenomics. More widely available offerings such as pharmacogenomics certificates, courses and continuing education offerings would help address the lack of education. One additional strategy would be for pharmacists to attain provider status, allowing for expanded roles in the implementation of pharmacogenomic services. As demonstrated by Smith et. al[26], many physicians prefer to consult a pharmacist and rely on the pharmacist's expertise in interpreting pharmacogenomic test results. Shifting patient identification, ordering, interpretation and follow-up duties to pharmacists would more efficiently and effectively allow incorporation of pharmacogenomic testing in routine clinical practice. Advocacy by clinicians (both physicians and pharmacists) will also be important for the adoption of pharmacogenomic tests in facilities that are not yet implementing a pharmacogenomic testing program.

Pharmacogenomic testing helps healthcare professionals provide patients with safer and more precise medication dosing, and in some cases more efficacious therapy selection. Of 14 queried facilities in the Upper Midwest and Big 10 network of schools, 10 facilities reported testing, and of those 10, no two facilities reported testing for the same set of genes. This lack of standardization across institutions may be considered a commentary on the barriers and challenges faced by facilities engaged in pharmacogenomic testing, as well as a

potential barrier itself due to the difficulty of compiling results among facilities that have different health outcomes resulting from different sets of genetic results. To address these challenges and to advance the field of pharmacogenomics, it is necessary for both pharmacists and clinicians to be educated on, and advocate for appropriate testing.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

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Acknowledgements: 2022 CPIC-PGRN Meeting. Poster presentation, "Routine Pharmacogenomic Testing in the Wisconsin Region." Kelsie Tingle, Paul Hutson, Emili Leary. 2022 UW-Madison Research Symposium. Poster presentation, "Routine Pharmacogenomic Testing in the Wisconsin Region." Kelsie Tingle, Paul Hutson, Emili Leary.

Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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Original Work

Retrospective Assessment of Sacubitril/Valsartan Prescribing Practices and Utilization in Patients With Heart Failure in a Rural Health System

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Abstract

Objective: The number of individuals diagnosed with heart failure is projected to increase in the coming years, and newer medications, such as angiotensin receptor-neprilysin inhibitors (e.g., sacubitril/valsartan) and sodium-glucose transport (SGLT-2) inhibitors (e.g., empagliflozin and dapagliflozin) have shown promising results in heart failure. The real-world prescribing practices of these newer medications warrant further investigation.

Methods: This retrospective descriptive study included reviewing electronic health records for 200 patients prescribed sacubitril/valsartan from January 1, 2015, to March 1, 2022. All patient records found to be eligible (n=163) underwent data abstraction through manual and electronic means. The primary outcome evaluated the prescribing patterns and use of sacubitril/valsartan in patients with heart failure. Secondary outcomes included whether the target dose of sacubitril/valsartan was achieved.

Results: At initiation of sacubitril/valsartan, approximately 2.5% (n=4) of study patients had a serum potassium of 5.2 mmol/L or greater, 2.5% (n=4) had an eGFR of less than 30 mL/min, and 11.9% (n=19) had a systolic blood pressure of less than 100 mmHg. Following initiation of sacubitril/valsartan, hypotension was reported in 51.5% of patients, which was the highest adverse drug reaction (ADR) identified. Dizziness, hyperkalemia, acute renal failure/acute kidney injury (AKI), cough, and angioedema were identified in 19.6%, 14.7%, 11.7%, 6.1%, and 1.8% of patients taking sacubitril/valsartan, respectively. No ADRs were identified in 30.7% of patients. The sacubitril/valsartan target dose was found to be achieved in 23.1% of all patients.

Conclusions: This study aligned with various findings from the PARADIGM HF trial and demonstrated that providers largely comply with recommended prescribing standards for sacubitril/valsartan. Adverse drug reactions seen after starting sacubitril/valsartan (e.g., decreased eGFR and systolic blood pressure, or increased serum potassium) may have influenced the titration of sacubitril/valsartan to target dose.

In the United States (US), more than 6 million adults have heart failure (HF), and that number is projected to dramatically increase in the coming years as the population ages.[1] Heart failure is one of the leading causes of hospital admission in the US, resulting in approximately 6.5 million hospital days annually.[2] Patients hospitalized for HF are at high risk of readmission.[2] Within 30 days of hospital discharge, nearly one in four patients with HF are readmitted, and almost half of those patients are readmitted within 6 months.[3] These cumulative events strongly predict mortality, and data from 2018 showed HF was mentioned on 13.4% of total death certificates in the US.[4] The high morbidity and mortality associated with HF is compounded by its significant cost burden.

Total costs associated with HF are estimated to be between $24 billion and $47 billion per year, with this number predicted to climb as HF prevalence grows.[2] Over the years, advances in HF treatment options, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta blockers (BB), and mineralocorticoid receptor antagonists (MRAs), have decreased mortality, decreased hospitalizations, lowered health care-associated expenditures, and improved quality of life.[2] Recent additions to the compendium of HF treatment options include the angiotensin receptor-neprilysin inhibitor (ARNi) sacubitril/valsartan, and sodium-glucose co-transporter 2 (SGLT-2) inhibitors (e.g., empagliflozin and dapagliflozin).

Sacubitril/valsartan is a combination of an angiotensin (II) receptor blocker (ARB) and a neprilysin inhibitor. Neprilysin is an

enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides.[5] In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, sacubitril/valsartan was shown to reduce cardiovascular death and HF hospitalization compared with enalapril in patients with chronic HF and a reduced ejection fraction.[6] Despite sacubitril/valsartan demonstrating significant mortality benefit in clinical trials and placement as first-line treatment for patients with HF with reduced ejection fraction (HFrEF) in the 2021 Guideline Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment, previous cornerstone, low-cost, effective pharmacotherapy options, such as ACEi, have largely continued to be used. However, cost analyses have consistently found sacubitril/valsartan to be a cost-effective treatment, with results being sensitive to the estimated reduction in mortality and the effectiveness associated with sacubitril/valsartan treatment.[5] This project was conducted prior to the most recent publication of the 2022 American Heart Association, American College of Cardiology, and Heart Failure Society of America (AHA/ACC/HFSA) Guidelines for the Management of Heart Failure.[7] A separate assessment of SGLT-2 inhibitor prescribing was conducted outside of this project.

Currently, there are no studies that assess the use and prescribing patterns of sacubitril/valsartan in a rural health care system in the US. Marshfield Clinic Health System, located in Wisconsin, is one of the largest rural, integrated health systems in the country. More than 2,000 patients are enrolled in the Marshfield Clinic Health System Heart Failure Improvement Clinic (HFIC) at any given time. Referrals to the HFIC come from hospitalists, cardiologists, and primary care providers. Pharmacy is consulted to perform comprehensive medication reviews prior to each patient's first HFIC appointment. This study is a retrospective cohort aimed to assess the prescribing patterns and utilization of sacubitril/valsartan in a rural physician group practice setting.

TABLE 1. Sacubitril/Valsartan Adverse Drug Reactions Gathered Manually

Angioedema	Dizziness
Hypotension	Acute renal failure/acute kidney injury
Cough	No ADRs reported

Methods

Design and Setting

A retrospective descriptive study was conducted by reviewing the electronic health records of all patients prescribed sacubitril/valsartan from January 1, 2015, to March 1, 2022, at a large tertiary care center in rural Wisconsin. Patients were screened for eligibility through multiple coding systems, including the International Classification of Diseases Ninth and Tenth Revisions (ICD-9/10), laboratory components, observations, the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System, and the Current Procedural Terminology (CPT-4) numeric coding system managed by the American Medical Association (AMA). Patients at any age were included if they had been diagnosed with any type of HF, which includes HF with reduced ejection fraction (HFrEF), defined as an ejection fraction of ≤ 40%; HF with mildly reduced ejection fraction (HFmrEF), defined as an ejection fraction of between 41% and 49%; and HF with preserved ejection fraction (HFpEF), defined as an ejection fraction of ≥ 50%, during the pre-specified timeframe using the "rule-of-one," and had taken or were currently taking sacubitril/valsartan. The "rule-of-one" was defined as having at least one distinct date associated with diagnosis of HF. Patients were excluded if they were found to have never started sacubitril/valsartan for reasons such as prohibitive costs/lack of insurance, if no prescription record of sacubitril/valsartan was found in electronic medical record, and/or if insufficient evidence was available to support a discernible timeframe of sacubitril/valsartan use (e.g., no evidence patient ever took sacubitril/valsartan, patient was lost to follow-up after one visit). This study was approved by the Institutional Review Board.

All eligible patients underwent data abstraction through both manual and electronic means. Patients' baseline characteristics, such as patient demographics (age, gender, and ethnicity), comorbid conditions (stroke, atrial fibrillation [A-fib], diabetes, hypertension, and myocardial infarction [MI]), laboratory values (serum potassium levels, estimated glomerular filtration rate [eGFR], brain natriuretic peptide [BNP], and N-terminal BNP), HF ejection fraction classification (HFrEF, HFmrEF, and HFpEF) prior to and after starting sacubitril/valsartan, and history of ACEi and/or ARB use were collected via the electronic database. Gathering of manual data included sacubitril/valsartan medication status (never started, started but discontinued, started and taken, and no record of sacubitril/valsartan use/prescription), factors affecting medication adherence/discontinuation (insurance coverage, cost, other, none or not applicable), most recent HF hospital admission date within the last 12 months prior to starting sacubitril/valsartan, first HF hospital admission date after starting sacubitril/valsartan, use of other HF medications (beta blockers, diuretics, mineralocorticoid receptor antagonists, and digoxin) within 30 days prior to starting sacubitril/valsartan, adverse drug reactions (ADRs) from sacubitril/valsartan (Table 1), medication changes that occurred based on side effects (no change, dose decrease, medication discontinuation), factors that could have affected side effect evaluation (drug interactions, contraindications, other medications started concurrently, other medications changed/take concurrently, other, or none of the above), and if the target dose of sacubitril/valsartan was achieved. Based on criteria from the PARADIGM-HF trial, hyperkalemia was defined as a serum potassium level of 5.2 mmol/L or greater and hypotension was noted if a patient had a systolic blood pressure of < 100 mmHg after starting sacubitril/valsartan.

Manually abstracted fields were collected using Computerized Medical Records (CMRs) and a REDCap database. REDCap is a secure web platform for building and

managing online databases and surveys. For this project, an internal database was used; access was given only to those with a valid REDCap account and who had been approved by the Institutional Review Board to review data as part of this study. Data downloaded from REDCap and electronically abstracted fields data was stored in a secure project management directory. The contents and access to this location are maintained by the Office of Research Computing and Analytics (ORCA) staff and complies with Marshfield Clinic Health System's archival procedures. Laboratory samples in this study were collected onsite and at other locations where the health system processes laboratory specimens.

The primary study objective was to evaluate the prescribing patterns and utilization of sacubitril/valsartan in patients with HF. Secondary objectives included whether the target dose of sacubitril/valsartan was achieved.

Statistical Analysis

Descriptive summaries were created to characterize the study cohort using standard descriptive statistics. Analyses were completed using SAS® version 9.4 (SAS Institute Inc.) statistical software.

Results

Of the 200 patients screened, 163 patients underwent analysis, and 37 were excluded. Among these eligible patients (n=163), 74.2% were male and 92% were Caucasian. Patients with HFrEF predominated the cohort, comprising 90.8% of patients, while HFmrEF was 8%, and HFpEF had the lowest percentage of patients at 0.6%. Of the total patients, 44.2% were enrolled in the HFIC. Patient characteristics at baseline preceding sacubitril/valsartan initiation are listed in Table 2 and Table 3. Comorbidities in addition to HF were assessed prior to the patient's initiation of sacubitril/valsartan. The most common comorbid condition was hypertension, which was observed in 86.5% of patients. Atrial fibrillation was the second most common comorbid condition, followed by history of myocardial infarction, observed in 55.2% and 45.4% of patients, respectively. Some characteristics that deviated from typical sacubitril/valsartan prescribing considerations included the

TABLE 2. Baseline Characteristics

Characteristic	*n*	*Mean*	*SD*	*Minimum*	*Maximum*
Age (years)	163	68	12.5	20	96
BMI (kg/m2)	93	30.5	6.9	15.5	50.4
Systolic Pressure (mmHg)	160	119.4	18.4	90	186
Diastolic Pressure (mmHg)	160	71.2	11.5	50	133
Heart Rate (bpm)	160	75.5	15.9	48	182
eGFR (mL/min)	161	61.6	17.7	12	90
Serum Potassium (mmol/L)	161	4.2	0.5	3.2	7.1
BNP (pg/ml)	137	1085.9	2224.4	5	16386
NT BNP (pg/ml)	12	3552.1	4326.2	175	11492

Abbreviations: BMI, Body Mass Index : eGFR, Estimated Glomerular filtration Rate; BNP, brain natriuretic peptide , NT BNP, N-terminal brain natriuretic peptide

TABLE 3. Additional Baseline Characteristics

Characteristic	*n*	*Percent (%)*
Male	121	74.2
Female	42	25.8
Ethnicity		
Caucasian	150	92
Other	13	8
History of ACE/ARB Use	146	89.6
Other Heart Failure Medications		
Beta Blockers	150	92
Diuretic	129	79.1
Mineralocorticoid receptor antagonist	71	43.6
Digoxin	23	14.1
Comorbid Conditions		
Stroke	14	8.6
Atrial Fibrillation	90	55.2
Diabetes	62	38
Hypertension	141	86.5
Myocardial Infarction	74	45.4
Heart Failure Ejection Fraction Classification		
HFrEF (LVEF ≤ 40%)	148	90.8
HFpEF (LVEF ≥50%)	13	8
HFmrEF (LVEF 41% - 49%)	1	0.6

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; LVEF, Left ventricular ejection fraction

following: approximately 2.5% (n=4) of patients had a serum potassium greater than 5.1 mmol/L, 2.5% (n=4) had an eGFR less than 30 mL/min, and 11.9% (n=19) had a systolic blood pressure less than 100 mmHg at drug initiation.

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were prescribed in approximately 89.6% of patients prior to starting sacubitril/valsartan. Among the other HF medications received before initiating sacubitril/valsartan, beta blockers were used in 92% of patients, diuretics in 79.1%, mineralocorticoid receptor antagonists (i.e., spironolactone, eplerenone) in 43.6%, and digoxin in 14.1%. The target dose of sacubitril/valsartan was found to be achieved in approximately 23.1% of all patients included in the analysis.

Hypotension was reported in 51.5% of patients, which was the highest ADR associated with the prescribing of sacubitril/valsartan. Dizziness was identified in 19.6% of patients, hyperkalemia in 14.7%, acute renal failure/acute kidney injury (AKI) in 11.7%, cough in 6.1%, and angioedema in 1.8% of patients. No ADRs were identified in 30.7% of patients. Some of the most common factors potentially influencing the development of ADRs included other medications being started concurrently (e.g., patient was started on spironolactone after sacubitril/valsartan was recently initiated, and then patient developed hyperkalemia) and concurrent medication dose adjustments (e.g., metoprolol dose increased at same time patient was started on sacubitril/valsartan and hypotension was noted). Factors impacting sacubitril/valsartan adherence/discontinuation for the entire population included ADRs, sacubitril/valsartan cost concerns/affordability, and lack of insurance coverage (18.4%, 11%, and 0.6%, respectively). The reason for sacubitril/valsartan discontinuation was not clearly identifiable in 67.5% of patients. When looking solely at patients prescribed sacubitril/valsartan but never started sacubitril/valsartan (n=14), cost was the main reason, comprising 78.6% of patients. Both lack of insurance coverage and ADRs were equivalent, with each category totaling 14.3%. For patients who started but ended up discontinuing sacubitril/valsartan (n=52), ADRs were the largest factor impacting discontinuation, for approximately 55% of patients, and medication cost was the second largest factor at 26.9%.

Discussion

This study revealed relevant considerations in prescribing practices and utilization of sacubitril/valsartan. Several baseline characteristics preceding initiation of sacubitril/valsartan had values that closely aligned with the PARADIGM HF pre-treatment group. In our study versus the PARADIGM HF trial, mean age was 68 years vs. 63.8 years, female sex was 25.8% vs. 21%, systolic blood pressure was 119.4 mmHg vs. 122 mmHg, heart rate was 75.5 beats per minute (bpm) vs. 72 bpm, BMI was 30.5 kg/m2 vs. 28.1 kg/m2, and hypertension was the most common comorbid medical condition prior to patients' initiation of sacubitril/valsartan. However, a number of patients in the baseline characteristics analysis had laboratory values that deviated from certain prescribing considerations.

Sacubitril/valsartan prescribing information includes a warning/precaution about development of hyperkalemia. Four patients had serum potassium level greater than 5.1 mmol/L at time of drug initiation in our study. Current findings are limited on sacubitril/valsartan use in patients with severe renal impairment, but our study included four patients with an eGFR of < 30 mL/min. Patients were also started on sacubitril/valsartan with systolic blood pressures of < 100 mmHg, although sacubitril/valsartan has been found to cause significant hypotension. Surprisingly, systolic blood pressure of < 100 mmHg contained the highest number of patients (n=19) compared to serum potassium and eGFR. One exclusion criteria in the PARADIGM HF trial was patients with a systolic blood pressure of < 100 mmHg at screening, and both the TRANSITION as well as PIONEER HF required patients to have a systolic blood pressure of at least 100 mmHg to demonstrate hemodynamic stability.[6,8,9] These findings contribute an overall view of what patient demographics, laboratory values, and comorbidities were prior to initiation of sacubitril/valsartan.

In this study, the majority of patients were found to have a history of ACEi or ARB use prior to sacubitril/valsartan initiation. The PARADIGM-HF trial required patients to receive an ACEi or ARB at stable doses equivalent to enalapril 10 mg daily with a duration of at least 4 weeks along with sequential run-in periods before randomization.[6] ACEi/ARB naïve patients have been included in previous landmark trials, such as the PIONEER HF and TRANSITION study, with results demonstrating comparable safety and efficacy in this sub-population.[8,9] Approximately 10% of patients in our study had no prior ACEi or ARB use prior to taking sacubitril/valsartan. Moreover, a large majority of the patients were on guideline-directed medication therapy (GDMT) for HFrEF, with beta blockers and diuretics having the top percentages (92% and 79.1%), and mineralocorticoid receptor antagonists being the third largest HF medication used (43.6%).

When analyzing safety outcomes, our study had high rates of hypotension and dizziness compared to other ADRs, which aligns with other clinical trial results. The PARADIGM HF trial showed a higher incidence of hypotension and symptomatic hypotension, but had a lower incidence of other ADRs, such as elevation in serum potassium, serum creatinine, or cough.[6] ADRs were noted to be the most common factor for non-adherence or discontinuation, while cost was the predominant factor deterring patients from starting sacubitril/valsartan. ADRs could be one of many factors that influenced sacubitril/valsartan dose titration.

We observed that both cost and ADRs still play a considerable role with adherence/discontinuation of sacubitril/valsartan. Although sacubitril/valsartan can be more cost prohibitive compared to ACEi, several studies have determined it is associated with high economic value. One study examined the cost-effectiveness of sacubitril/valsartan relative to ACEi for the treatment of HFrEF, with clinical probabilities based predominantly on the PARADIGM HF trial.[10] It found that sacubitril/valsartan was both more costly and effective over a lifetime, yielding $50,959 per quality-adjusted life-years (QALY) gained versus ACEi.[10] Treatment duration was a crucial contributing factor and at 3 years of follow-up, the QALY gained was approximately $250,000. Another study similarly reported that compared to an ACEi, sacubitril/valsartan use derives $45,017 per QALY

gained.[11] Additionally, it concluded that patients with HFrEF could derive cost benefits from additional life expectancy and lower rates of hospitalizations from sacubitril/valsartan use.[11] Overall, the decision must be made as to whether the extra benefit of sacubitril/valsartan seen in PARADIGM HF (e.g., cardiovascular mortality, HF hospitalization rates) outweighs the upfront drug costs.

This study has several limitations. First, it is retrospective in nature, making it more prone to confounding variables. Another limitation of this study is that patient adherence was unable to be confirmed or followed. Gaps in care can be difficult to determine, especially if patients are being seen at multiple health care facilities. Generalizability of this study is reduced due to the smaller sample size confined to one health system, the small number of ethnically diverse patients, and the population mainly consisting of males. Strengths for this study include having verified coding systems to evaluate data, analyzing relevant endpoints that were influenced by the PARADIGM HF trial design, and conducting a real-world study.

Conclusion

This study aligned with several PARADIGM HF trial findings, although there was not a comparison group. Similarities were shown with baseline patient characteristics prior to sacubitril/valsartan initiation. Our data demonstrated that providers prescribing sacubitril/valsartan mainly comply with recommended standards such as having a serum potassium of less than 5.2 mmol/L before starting sacubitril/valsartan. However, there were a few deviations noted in terms of eGFR, serum potassium, and systolic blood pressure prescribing patterns. These factors could be influencing the adverse drug reactions seen after starting sacubitril/valsartan and should be considered before patients are prescribed this medication, as a large proportion of patients attributed adherence/discontinuation to these unfavorable affects (e.g., hypotension, hyperkalemia, dizziness). The large majority of patients are also being prescribed sacubitril/valsartan with a reduced ejection fraction HF classification and are mostly on additional GDMTs. Overall, cost barriers were noted in a relatively small number of patients (11%), especially compared to ADRs, which could indicate that patients are having fewer difficulties with affordability and could lead to greater uptake in future prescribing practices of sacubitril/valsartan considering the health care-associated cost benefits.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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Review Article

Risk of Acute Kidney Injury with Sodium-Glucose Cotransporter-2 Inhibitors in Elderly and Very Elderly Adults Compared to the General Adult Population

by Kenina E. Silvera, 2024 PharmD Candidate, Michael W. Nagy, PharmD, BCACP

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are used to treat type 2 diabetes mellitus (T2DM) by inhibiting the reabsorption of filtered glucose in the proximal convoluted tubules of the kidney, promoting urinary excretion of glucose. The five SGLT2 inhibitors approved by the FDA are: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin.[1] Some of these agents have additionally gained approval for the use in other disease states, including heart failure and chronic kidney disease (CKD).

Question

In the general adult population, elderly adults, and very elderly adults, what is the risk of acute kidney injury (AKI) with sodium-glucose cotransporter-2 (SGLT2) inhibitors versus placebo?

While these agents largely have shown long-term benefits of kidney protection, there has been controversy regarding the risk for AKI, which is defined by the Kidney Disease Improving Global Outcomes (KDIGO) guideline as an increase in serum creatinine (SCr) by ≥0.3 mg/dL within 48 hours, or an increase in SCr ≥1.5 times baseline presumed within 7 days.[2]

The concern for AKI rose after an increased number of reports to the FDA adverse event report system, with 101

TABLE 1. Published Meta-Analyses on the Association Between SGLT2 Inhibitors and the Risk of AKI Versus Placebo

Authors	Study Population	Baseline Age, Years	Studies Included in AKI Calculations	Patients Analyzed with AKI Results, n	Results on Risk of AKI, Ratio (95% CI)
Donnan et al.[7]	Patients with T2DM	NR	Bailey et al.[14] (2012) Bailey et al.[15] (2013) Cefalu et al.[16] Kohan et al.[17] Leiter et al.[18] Malodonado-Lutomirsky et al.[19] Softeland et al.[20] EMPA-REG Outcome[21]	10,651	RR 0.59 (0.39-0.89)
Gilbert et al.[8]	Patients with T2DM	NR	EMPA-REG Outcome[21] CANVAS[22] DECLARE-TIMI 58[23]	28,490	HR 0.66 (0.54-0.80)
Salah et al.[9]	Patients hospitalized with AHF or within 3 days of discharge with AHF	Mean: 69.9	SOLOIST-WHF[24] EMPULSE[25]	1,740	OR 0.76 (0.50-1.16)
Kaze et al.[10]	Patients with DKD	Median: 65.2	CANVAS[22] CREDENCE[26] EMPA-REG Outcome[21]	15,744	RR 0.85 (0.66-1.11)
Rigato et al.[11]	Elderly patients with T2DM	NR	DECLARE-TIMI 58*[23] DAPA-CKD[27] CREDENCE[26] Leiter et al.*[28] EMPA-REG Outcome*[21]	Age ≥ 65: 15,344 Age > 75: 1,819	Age ≥ 65: RR 0.73 (0.62-0.87) Age > 75: RR 0.59 (0.37-0.94)

*AKI = acute kidney injury, T2DM = type 2 diabetes mellitus, AHF = acute heart failure, DKD = diabetic kidney disease, NR = not reported, HR = hazard ratio, OR = odds ratio, RR = risk ratio, * = included in calculations for patients > 75*

confirmable cases from March 2013 to October 2015 regarding AKI following SGLT2 inhibitor initiation, some requiring hospitalization and dialysis.[3] About half of the cases occurred within 1 month of SGLT2 inhibitor initiation, with most patients improving with cessation of the agent. Some patients were dehydrated, hypotensive, or taking other agents that can have renal effects. Mechanistically, this concern for AKI is plausible, particularly due to the possibility for osmotic diuresis and volume depletion, which if not prevented have the potential to induce AKI. Additionally, increased sodium delivery to the macula densa leads to increased afferent arteriole constriction and decreased GFR, which could lead to renal ischemic injury.[4,5] While a modest eGFR "dip" of 3-5 mL/min/1.73 m^2 on average with initiation of an SGLT2 inhibitor is common, the class of agents has consistently demonstrated long-term renal protection, similar to that in renin-angiotensin-aldosterone-system inhibitors.[4,5] However, these potential mechanisms of AKI could be particularly concerning in elderly (≥65 years) and very elderly (≥75 years) patients, who are at a greater baseline risk of AKI due to physiologic changes in the aging kidney, use of concomitant nephrotoxic medications, and being more susceptible to volume depletion.[6]

Literature Review / Evidence Summary

A literature search was performed using PubMed with the following terms or their combinations: "acute kidney injury," "AKI," "SGLT2," "elderly," and "safety."

Four meta-analyses in the general adult population concluded no increased risk of AKI with SGLT2 inhibitors, with two meta-analyses concluding a decreased risk of AKI, which is shown in Table 1.[7-10] Though the meta-analysis by Donnan et al. showed a decreased risk of AKI (RR 0.59; 95% CI: 0.39-0.89), evidence for decreased risk is heavily weighted by the EMPA-REG Outcome trial, and the pooled estimate is considered non-significant with removal of this trial (RR 0.48; 95% CI: 0.14-1.64).[7] The meta-analysis by Gilbert et al. similarly showed a decreased risk of AKI, also including the EMPA-REG Outcome trial, though weighting of each trial was not reported.[8] Salah et al. analyzed safety outcomes of starting SGLT2 inhibitors in patients hospitalized with acute heart failure or within three days of discharge, with an average patient age of 70 years, showing no increased risk of AKI with SGLT2 inhibitors versus placebo (OR 0.76; 95% CI: 0.50-1.16).[9] This result in a population particularly vulnerable to AKI with an older average age further contributes to the safety profile of SGLT2 inhibitors.

Rigato et al. specifically analyzed the safety profile of SGLT2 inhibitors in elderly patients with T2DM, showing decreased risk of AKI with SGLT2 inhibitors in patients ≥65 years (RR 0.73; 95% CI: 0.62-0.87).[11] Adults older than age 75 accounted for < 10% of the meta-analysis population, with 1,819 patients older than 75 out of a total population of 19,986 patients. Though the three randomized controlled trials (RCTs) that reported rates of AKI for patients older than 75 individually showed no significant difference in rates of AKI between SGLT2 inhibitors and placebo, when pooled, a decreased risk of AKI with SGLT2 inhibitors was found (RR 0.59; 95% CI: 0.37-0.94).[11] The authors did note that RCTs typically do not stratify adverse effects by age, and the data obtained from supplement and post-hoc analysis was often incomplete and fragmented.[11] Notably, every meta-analysis was limited due to AKI in RCTs largely being reported as an adverse effect rather than a primary or secondary outcome. This means data on AKI may not have been systematically collected with variations in reporting between trials.

The 2023 American Diabetes Association Standards of Care in Diabetes guideline states that though there was initial concern for risk of AKI with SGLT2 inhibitors, this has not been found to be true in RCTs of patients with or without advanced kidney disease, regardless of use of diuretics or other medication that may reduce GFR.[12] The 2022 KDIGO Diabetes Management in CKD guideline states that despite the theoretical concern for AKI with SGLT2 inhibitors, clinical trials have shown a decreased incidence of AKI with SGLT2 inhibitor initiation.[13] However, in patients with tenuous volume status, the KDIGO guideline also states that it may be reasonable to reduce the dose of diuretics with SGLT2 inhibitor initiation out of an abundance of caution, with follow-up arranged to monitor. To prevent premature discontinuation of SGLT2 inhibitors, an acute decrease of less than 30% in eGFR should be tolerated. If there is a decline in eGFR of greater than 30%, volume status should be optimized, any other nephrotoxic agents should be discontinued, and alternative etiologies for AKI should be evaluated.[13]

Evidence-Based Answer

Despite earlier FDA warnings, SGLT2 inhibitors are not associated with an increased risk of AKI in adult, elderly, and very elderly populations (strength of recommendation = A, based on multiple, consistent, patient-oriented meta-analysis of high-quality studies). More data is needed to explore the potential for decreased risk of AKI with SGLT2 inhibitors, with rates of AKI studied as a primary or secondary outcome.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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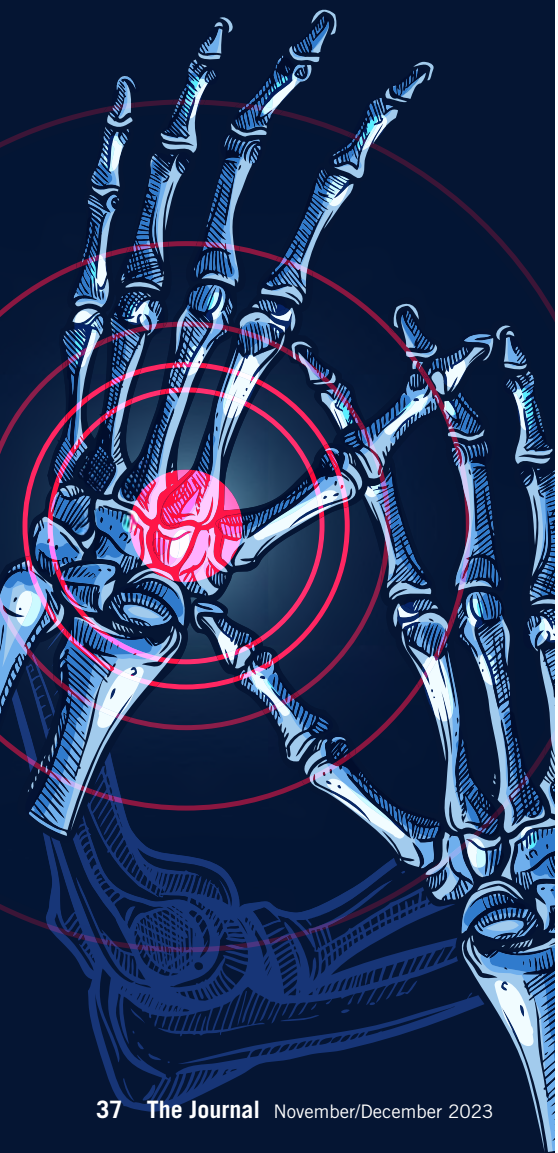
Review Article

Rituximab: A Review of Use in Adult Rheumatology

by Kenina Silvera, 2024 PharmD Candidate, Diane Oddis, BPharm, BCPS, William Krombholz, PharmD, Amy Gorgen, BPharm



Though rituximab was originally approved for treating non-Hodgkin's lymphoma, its use has expanded to a variety of disease states, including immune-mediated rheumatic diseases.[1] This literature review aims to summarize recommendations for rituximab use in adults with rheumatic diseases that have American College of Rheumatology (ACR) or European Alliance of Associations for Rheumatology (EULAR) guidelines available. Additionally, this review aims to briefly summarize evidence and dosing for rituximab in each disease state, as well as the available formulations.

Introduction

Rituximab is a chimeric anti-CD20 monoclonal antibody (mAB) first approved for the treatment of non-Hodgkin's lymphoma in the US in 1997 under the brand name Rituxan®.[1] CD20 is a transmembrane protein expressed by the majority of pre-B and mature B-cells.[2,3] Rituximab, as an anti-CD20 mAB, depletes CD20+ B-cells through multiple mechanisms, including antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.[3]

Since 1997, rituximab has been used in numerous disease states, particularly finding use in immune-mediated rheumatic diseases, such as rheumatoid arthritis (RA), Felty syndrome, systemic lupus erythematosus (SLE), Sjogren's syndrome (SjS), and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides.[4] Of these disease states, rituximab is only FDA approved for rheumatoid arthritis and the Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitides microscopic polyangiitis and granulomatosis with polyangiitis. Though not well elucidated, there are a variety of mechanisms thought to contribute to the efficacy of rituximab in immune-mediated rheumatic diseases, including the reduction of autoantibodies and the depletion of pathogenic subsets of CD20+ B-cells. For example, in RA, this includes the reduction of rheumatoid factor (RF) and the depletion of CD27+IgD- B-cells, which have a greater prevalence in the synovial fluid and are more prone to expressing the cytokine RANKL after activation, contributing to bone resorption.[5,6]

Formulations

Since the approval of Rituxan®, biosimilars have come to market, such as Truxima® (rituximab-abbs) in 2018, Ruxience® (rituximab-pvvr) in 2019, and Riabni® (rituximab-arrx) in 2020.[7] Biosimilars are copies of biological drugs, though molecular identity cannot be established as it can be with generics of chemical drugs.[8] These biosimilars are commonly used in practice in lieu of Rituxan®, often depending on insurance coverage, and may offer substantial cost savings for patients, which can be expanded through co-pay assistance programs. A subcutaneous formulation, Rituxan Hycela®, was approved in 2017 for several types of cancer after at least one IV infusion of rituximab, though it has not yet been studied in rheumatic disease.[9] Further research is needed to compare the efficacy and tolerability of the subcutaneous formulation in this patient population, as it could increase patient convenience and decrease time for treatment and monitoring.

Rheumatoid Arthritis

RA is a chronic, inflammatory autoimmune disease that principally affects the joints, though it can progress to systemic effects. Damage to the joints often results in bone erosion and deformities which are associated with significant pain.[10]

Rituximab is categorized as a biologic disease-modifying anti-rheumatic drug (DMARD) which was first approved in 2006 for use in RA. The 2022 EULAR and the 2021 ACR guidelines on the treatment of RA generally recommend the addition of a biologic DMARD after failure to achieve goals of treatment on at least one conventional synthetic DMARD, such as methotrexate or leflunomide, with short-term glucocorticoids.[11,12] The decision to try more than one conventional synthetic DMARD is typically dependent on treatment cost and whether poor prognostic factors are present, such as high disease activity or high levels of RF.[11,12] The choice of biologic DMARD is largely based on patient-specific factors, with rituximab being preferred in patients with a history of a lymphoproliferative disorder where rituximab is an approved treatment. In this patient population, rituximab can be considered earlier in therapy if disease activity is moderate to high.[11]

When rituximab was approved for RA in the US, dosing recommendations for one course were two 1,000 mg doses separated by two weeks, with subsequent courses given every 24 weeks or as clinically indicated, but no sooner than 16 weeks.[3] The EULAR guideline, based on the most recent expert consensus in 2011, prefers a low-dose regimen of either a single 1000 mg IV infusion or two 500 mg IV infusions separated by two weeks.[12,13] This is reinforced by a more recent meta-analysis comparing the efficacy of initiating low-dose (1 x 1000 mg or 2 x 500 mg) versus high-dose (2 x 1000 mg) rituximab in patients with RA. Primary endpoints included ACR criteria for 20% improvement (ACR20), ACR50, and ACR70, in disease activity, as well as the Disease Activity Score in 28 joints (DAS28) at both 24 and 48 weeks. Non-inferiority criteria were met for low-dose rituximab for the ACR20, ACR50, and DAS28 at 24 and 48 weeks. There were no significant differences between the primary endpoints.[14]

However, per the expert consensus, in patients with a history of TNF-inhibitor failure, the FDA-approved high dose is preferred. Monitoring for radiographic progression with the low-dose regimen was not evaluated in this population, while the higher-dose regimen has shown efficacy in slowing radiological damage at both one and two years of treatment per the REFLEX trial.[13,15,16]

Though the optimal strategy for dosing frequency is not clearly defined, the ACR and EULAR guidelines generally recommend the treat-to-target strategy over regular re-treatment, with goals of sustained clinical remission or low disease activity.[11-13] The treat-to-target strategy is preferred to optimize therapy, prevent over- or under-treatment, and improve patient outcomes.[13,14]

Felty Syndrome

Felty syndrome is an uncommon condition characterized by a triad of RA, splenomegaly, and neutropenia that most commonly affects patients with severe, erosive, long-standing, seropositive arthritis.[17]

Based on limited case studies, there is best evidence for the use of the DMARDs methotrexate and rituximab, both of which have shown the potential to improve neutrophil counts in this subset of patients. Rituximab is recommended to be added after insufficient response to methotrexate, a conventional synthetic DMARD, per the EULAR and ACR guidelines outlined above.[12,13,17,18]

Systemic Lupus Erythematosus

SLE is a heterogeneous autoimmune disease with a wide array of systemic manifestations; two of the most common are acute cutaneous lupus and arthritis.[19] Due to this heterogeneity, treatment is largely dependent on symptoms, organ involvement, and level of severity.[19,20]

The 2019 EULAR guideline for the management of SLE recommends rituximab in severe, refractory cases of organ-threatening, non-renal SLE. For SLE with renal involvement, rituximab can be considered in relapsing or refractory disease.[20] These recommendations are based on a lack of evidence for efficacy earlier in the disease process (e.g. less severe disease) or not having failed first-line options.[20-23]

The randomized-controlled EXPLORER trial in patients with moderate-to-severe non-renal SLE found no significant differences in clinical response between rituximab and placebo when added to the standard of care.[21-22] In Hispanic and Black patients, however, a significant difference was found in both partial and complete clinical response with rituximab versus placebo ($p = 0.04$).[22] The randomized-controlled LUNAR trial in patients with class III or IV lupus nephritis found no significant differences in clinical renal response between rituximab and placebo when added to the standard of care.[23] Despite the findings in these two trials, retrospective studies have found benefit in using rituximab in more severe, refractory cases of both renal and non-renal SLE.[21]

In studies, rituximab regimens have included two 1000 mg doses two weeks apart as well as four doses of 375 mg/m2/week.[21] Though not formally compared, differences in response have not been noted between the two regimens.[24] As with RA, a treat-to-target strategy may offer greater benefits in decreasing the frequency and severity of flares.[19]

Sjogren's Syndrome

SjS is a systemic autoimmune disease leading to dysfunction of secretory glands, causing mucosal dryness, particularly in the eyes and mouth, known as sicca symptoms. Approximately 50% of those affected may develop extra-glandular involvement with a wide spectrum of clinical manifestations, affecting a multitude of organ systems. A variety of autoantibodies are also associated with SjS, including antinuclear antibodies, anti-Ro/SS-A, and cryoglobulins. Additionally, SjS often occurs with other systemic autoimmune diseases, including RA and SLE.[25,26]

While therapy is primarily directed at symptomatic relief of sicca symptoms, systemic therapies can be considered in patients with active systemic disease. The 2019 EULAR guideline for the management of SjS developed algorithms through task force clinical experience and largely retrospective studies based on domains affected and disease severity.[26] To briefly summarize the place of rituximab in these algorithms, rituximab is considered a second-line option in SjS with the following: cutaneous vasculitis with high activity (diffuse purpura covering ≥18% of the body surface area or the presence of ulcers), renal involvement with a high EULAR Sjögren's syndrome disease activity index (ESSDAI) domain score (≥15), multineuritis, and hemolytic anemia with hemoglobin levels <8 g/dL. Rituximab is considered as rescue therapy, after first- and second-line treatments, for SjS with the following: acute glandular involvement, arthritis with synovitis and high severity (ESSDAI domain score >5 or severe widespread tenosynovitis), interstitial lung disease with symptoms present with ordinary activity or at rest, and central nervous system (CNS) vasculitis or neuromyelitis optica spectrum disorder. Though algorithms vary based on organ involvement, generally, glucocorticoids are first-line, with other oral immunosuppressants second-line, or as second-line options. Rituximab may be preferred over alternative second-line therapies, such as oral immunosuppressants, or other rescue therapies in patients with cryoglobulinemic-associated vasculitis (CV).[26]

While most uncontrolled trials for the use of rituximab in SjS have demonstrated

benefit in either global response, organ-specific response, or reduction of prednisone, two major randomized-controlled trials, the TEARS and TRACTISS trials, exhibited underwhelming results.[27,28] The TEARS trial found no significant differences between placebo and rituximab in the primary outcome of ≥30 mm improvement in two out of four visual analog scales (VAS) for global disease, fatigue, pain, and dryness at 6 months.[27] Notably, at baseline, patients had only moderate global disease activity with an average ESSDAI score of 10.1. The TRACTISS trial also found no significant differences between placebo and rituximab in the primary outcome of a decrease in ≥30% in VAS assessments of fatigue or oral dryness at week 48.[28] However, there was a significant difference in EEDAI scores at week 36. At baseline, patients had low global disease activity with an average ESSDAI score of 5.7.

The best evidence for use of rituximab is for patients with CV. In a retrospective trial of patients with cryoglobulinemia or vasculitis, there was a significant change in ESSDAI score from baseline to six months, with an average baseline ESSDAI score of 24 and average score at six months being 14.5 ($p = 0.008$), which aligned with results of previous studies in this population.[26,29]

The 2019 EULAR guideline recommends two 1000 mg doses two weeks apart for induction, as that dosing was used in the majority of studies.[26] However, no recommendations are made regarding maintenance use of rituximab or dosing. There is a paucity of data examining maintenance dosing and frequency of rituximab in patients with SjS.

Antineutrophil Cytoplasmic Antibody-Associated Vasculitides

ANCA-associated vasculitides are a rare group of autoimmune, necrotizing vasculitis with systemic, heterogeneous effects. This group includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[30] While GPA and MPA are classified as different diseases, they are often combined in guideline recommendations due to pivotal trials investigating these diseases jointly.[31]

For induction of remission for patients with active GPA or MPA that is not organ- or life-threatening, the 2022 EULAR guideline on the management of ANCA-associated vasculitides recommends glucocorticoids in combination with rituximab first-line.[32] This recommendation is extrapolated from trials that included patients with non-organ-threatening vasculitides, showing similar efficacy and safety to those with more severe disease at baseline. No randomized controlled trials have been performed comparing rituximab to other agents in patients with non-organ- or non-life-threatening vasculitides.[32] In contrast, the 2021 ACR guideline on the management of ANCA-associated vasculitides recommend methotrexate preferentially over rituximab in combination with glucocorticoids due to the reported greater body of evidence and clinical experience with methotrexate, noting clinical trials are needed to compare their efficacy.[31]

For induction of remission in organ- or life-threatening GPA or MPA, the EULAR guideline recommends either rituximab or cyclophosphamide in addition to glucocorticoids, with rituximab preferred in relapsing disease.[32] The EULAR guideline also notes rituximab is often preferred over cyclophosphamide in practice due to the risks of infertility, malignancies, and bone marrow failure associated with cyclophosphamide. For these reasons, the ACR guideline explicitly recommends rituximab over cyclophosphamide for induction therapy in patients with organ- or life-threatening GPA or MPA.[31]

In maintaining remission of GPA or MPA, the EULAR guideline recommends rituximab for all patients.[32] The ACR guideline recommends rituximab for maintenance in patients with organ- or life-threatening disease.[31] However, in patients with non-organ- or non-life-threatening GPA, rituximab is only recommended as an option for maintenance in patients who received either rituximab or cyclophosphamide for induction therapy.

Due to a lack of trials involving rituximab in the treatment of EGPA, rituximab is used less frequently. The EULAR guideline recommends rituximab as a second-line alternative to cyclophosphamide in inducing remission in organ-threatening disease and as an option for maintaining remission.[32]

For EGPA, the ACR guideline recommends rituximab or cyclophosphamide for induction in organ- or life-threatening disease, with preference for cyclophosphamide in patients with active cardiac involvement.[31] This is due to the increased risk of mortality in this population and greater evidence for cyclophosphamide. In patients with non-organ- or non-life-threatening EGPA, rituximab is only recommended

to be considered for induction after failure of preferred agents, which include mepolizumab, methotrexate, azathioprine, and mycophenolate mofetil. For all patients with EGPA, the ACR guideline only recommends considering rituximab for maintenance therapy if remission was induced with rituximab.[31]

Induction dosing is recommended as a course of four 375 mg/m2/week doses or a course of two 1000 mg doses 14 days apart.[31,32] A recent meta-analysis of retrospective studies found no difference in safety or efficacy between these doses.[32,33] For maintenance of remission, a single dose of 500 mg every 6 months is generally recommended. In patients who relapse on this maintenance regimen, an increase in dose to 1000 mg or an increase in frequency to every 4 months can be considered.[31]

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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2023 PSW Annual Meeting

2023 PSW Annual Meeting Recap

by Grayson Cooley, 2024 PharmD Candidate, Anna Erickson, 2024 PharmD Candidate, Clara Nickel, 2024 PharmD Candidate

In the spirit of "Soaring to New Heights," more than 270 pharmacists, technicians, and students gathered at the La Crosse Center for the 2023 PSW Annual Meeting. Attendees participated in a three-day conference on August 24-26 focused on education, professional advancement, and intraprofessional collaboration. The 2023 meeting was held in person, with opportunities to view on-demand recordings of select live sessions. The top-notch educational programming ranged from topics related to the implementation of a pharmacogenomic practice model to the introduction of the PSW opioid toolkit. Audience participation was facilitated by the PSW app, where attendees could view presenter biographies, create a personal agenda, and earn points by entering codewords provided at each session. Participants were able to network with other attendees by posting updates on the activity wall and connecting and messaging each other through the app.

The 2023 Annual Meeting opened on Thursday evening with a welcome reception at the Riverside Terrace, where the focus was on connection with both new and familiar colleagues and friends. Official programming began on Friday morning with certified professional speaker Matt Booth, who described how simple changes in outlook can lead to a "basically incredible" life. He encouraged listeners to transition from the classic conversation starter of "How are you?" to asking someone to "tell me something good," as these few words can radically change an interaction and create a more positive experience for everyone involved. He explained that positivity is not solely about your attitude but also how you communicate with others. The eight dimensions of wellness and a review of the mental health continuum were discussed by a panel featuring Kathy Chambers, Jessa Kinnamon, and moderator Ellina Seckel. The speakers addressed ten practical tips for supporting wellness based on their experience working with employees across the spectrum of mental health in positions from crisis to thriving. Actions such as spending time in nature or practicing gratitude can promote and set the course toward a more fulfilled and purposeful life.

Following the forums was an Exhibit Showcase, where more than 50 exhibitors provided information on new and innovative products and projects that are currently changing the practice of pharmacy. During this time, attendees were also able to attend the annual Poster Session, featuring research from student pharmacists, residents, and practitioners. The 24 posters included topics from medication safety to the implementation of new monitoring protocols, all under the theme of promoting practice advancement and taking our profession to new heights.

Early afternoon highlighted two exhibit theaters, "Management of Factor Xa Inhibitor-Related Life-Threatening or Uncontrolled Bleeding" hosted by AstraZeneca's Tim Cober and "Operationalizing Care Delivery in Pharmacy with Workflow Services" facilitated by Laura Brown and Matt Huppert. The remainder of the afternoon was filled with two to three simultaneous presentations every hour. The first round included:

- "Advancing Quality of Care and Administrative Efficiency Through Electronic Health Information Exchange," by Joe Kachelski
- A discussion on healthcare trends, their impact on pharmacy, and the role of technology in pharmacy practice in "ASHP Foundation Pharmacy Forecast 2023: Strategic Planning Guidance for Pharmacy Departments in Hospitals and

Health Systems" by Brianne Bakken and Justin Konkol
- "Leveraging Quality Metrics to Highlight the Impact of Ambulatory Care Pharmacy" by Jennifer Foti, Tiffany Kremmer, Francesca Johnson, and Drea Maier, which explained the use of quality metrics and their importance in the ambulatory care setting

The second round of presentations included:

- Annmae Castaneda and Patricia Gonzalez Clark's presentation "Addressing Social Determinants of Health by Overcoming Language Barriers in Community Pharmacy for Underserved Communities," which detailed the importance of interpreter services in pharmacies and resources to implement an interpreter service
- "Improving Safety and Efficiency Around Ordering Total Parenteral Nutrition" by Jaclyn Moeller, Megan Ose, and Sarah Seward, which explained the use of technology in the ordering process to prevent errors specifically in TPN orders
- Matt Palmer's "Insulin & Diabetes Management in Seniors and Senior Living Care Venues," focused insulin safety measures to consider in healthcare facilities

The Friday afternoon presentations were rounded out with:

- "Making the Case: Implementing Pharmacogenetic Clinical Services" by Emili Leary and Carolyn Oxencis, describing the how pharmacy teams can implement a precision medicine service at their practice
- "Pediatric Pearls" was moderated by Brianne Bakken and a team of pediatric pharmacists from Children's Wisconsin detailing advice for medication administration, monitoring, and use in the pediatric population

Friday night was spent in the Arena of the La Crosse Center for the Friday Night Party, which was decorated with an Oktoberfest theme.. Our Wisconsin pharmacy family was joined by the Oktoberfest Royal Family who showed us the "spirit of fest." These folks led the way during the celebration and brought Gemütlichkeit and cheer to the community with an emphasis on charity. It was a night filled with fun games, loud laughter, and impressive polka dancing.

Saturday morning included:

- Lieutenant Commander Christopher Frazer, Helene McDowell, Sashae Silas, Nelly Veliz, and Mo Yang discussing "Cultural Uniqueness: Elevating Perspectives, Inspiring Change" in which they emphasized barriers faced by patients from different cultures and ethnicities and offered examples of best practices for culturally sensitive pharmacy care
- "Advocating for Care Transformation and Innovation" by Kate Hartkopf, Helene McDowell, Sarah Sorum, Kari Trapskin, and Danielle Womack, discussing the grant work underway at PSW and pathways to engage in PSW advocacy, grant work, and other activities
- PSW Presidential remarks from President Hannet Tibagwa Ambord

Everyone in attendance agreed that Tibagwa's words were kind and powerful, filled with hope, truth, and love. Her dedication to both her family and pharmacy alike may have caused a few tears to be shed in the conference hall that morning. It was a great way to start off the final day of the conference.

Three simultaneous presentations kicked off the afternoon programming:

- Julie Thiel and Trisha Seys Ranola discussed various lifestyle practices and techniques to aid in "Creating Your Best Life."
- Clara Nickel and Matt Huppert gave an informative and detailed presentation on the "Creation and Implementation of Diabetes Self-Management Education in an Independent Community Pharmacy" setting.
- Stacy Reid discussed professional identity formation (PIF) in her presentation, "Professional Identity Formation: What To Know When Working with Students."

The second time slot in the afternoon provided three additional presentations:

- "Beyond the Prescription Pad: Team Roles in Optimizing Parkinson's Disease Management" presented by Rachel Biemiller, Kelly Cieslak, Joy Cochran, Diane Erdman, Zachary Hovis, and Ronald Mohorek summarized the roles of different team members in Parkinson's disease management and various treatment options.
- Matt Huppert, Mark O'Connell, and Janvi Shah presented, "Collaborating Locally to Address the Opioid Epidemic: Introducing the Opioid Toolkit."
- Amanda Margolis and Sarah Pagenkopf presented on updates to continuing professional development for those with board certification in "BPS Re-certify Ready? CPD: Tracking & Managing Continuous Professional Development."

The last afternoon time block of the 2023 PSW Annual meeting brought two presentations and the Wisconsin pharmacy residency showcase.

- Sura AlMahasis and Martha Mauer's presentation, "Overdose 2 Action: Using Best Practice Altering to Direct Patient Care," detailed best practice alerts (BPAs) and their use in the opioid epidemic.
- Emma Dreischmeier, Madelyn Fischer, and Cassie Sedgwick summarized important clinical information in the "Toolkit Spotlight: Mental Health: Depression & Anxiety and COPD Toolkit."

Closing out the afternoon was the residency showcase, which offered students the opportunity to interact and connect with 19 pharmacy residency programs from across Wisconsin.

The 2023 PSW Annual Meeting truly showed how pharmacy has "soared to new heights" in recent years. Implementation of new programs in the community setting, toolkit creations, professional identity development, and research in pharmacy best practices shows the advancement of pharmacy as a profession. Best of all, Wisconsin pharmacy professionals are leading the charge in many of these areas, and shared their insight with colleagues at our annual conference this summer!

Grayson Cooley, Anna Erickson, and Clara Nickel are 2024 Doctor of Pharmacy Candidates at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

2023 PSW Fellowship Recipients

The PSW Fellowship Program (FPSW) exists to formally recognize PSW members who have demonstrated engagement with and sustained and substantive contribution to PSW. Candidates achieve this recognition through formal and informal leadership in PSW and advancing patient care and the practice of pharmacy in the state of Wisconsin in any practice setting. Fellows will be recognized annually at the PSW Annual Meeting. Learn more about this program on the **PSW website**.

Below (left to right): *2023 PSW Fellowship Recipients Nicholas Olson, Al Loeb (Distinguished Service Awardee) and Arlene Iglar. Sarah Sorum is the CEO of the Pharmacy Society of Wisconsin.*

PSW Award Recipients

The 2023 PSW Award recipients were recognized at the PSW Annual Meeting Awards Banquet on Saturday, August 26, 2023.

Distinguished Service
Al Loeb, RPh, MS
Retired

Pharmacist of the Year
Jeffrey Fish, PharmD, FCCM, BCCCP

Bowl of Hygeia
Nicole Schreiner, PharmD

Young Pharmacist of the Year
Francesca Napolitano Johnson, PharmD, MEd

Excellence in Innovation
William Peppard, PharmD, BCPS, FCCM

Curtis A. Johnson Award
Brianne Bakken, PharmD, MHA
Assistant Professor
Medical College of Wisconsin, Milwaukee

Interdisciplinary Care Partner
ED MAT-Link Team: MCW, West Allis Fire Department, & Community Medical Services

Interdisciplinary Care Partner
Christopher D. Fletcher, MD

Pharmacy Technician of the Year
Randi Lindberg, CPhT

Student Achievement Awards
Sara Wright (Concordia University Wisconsin)
Rachel Schneider (Medical College of Wisconsin)
Chelsea Moyer (University of Wisconsin-Madison)

WPQC Award Recipients

WPQC Engagement Award
Wausau Family Pharmacy

WPQC Innovation Award
Gretchen Kunze
Gundersen Pharmacy: Cass Street

WPQC Innovation Award
Cassy Cichy
Lakeview Pharmacy

WPQC Engagement Award
Hartig Drug

UNIVERSITY OF WISCONSIN-MADISON SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Business Member Spotlight: Taylor Mancuso

by Caroline Paley, 2024 PharmD Candidate, Charisse Yan, 2025 PharmD Candidate

As a medication safety pharmacist, Taylor Mancuso, PharmD, CPPS, is fortunate to practice in a dynamic and highly collaborative environment. While pursuing her PGY-1 residency at Ascension/Wheaton Franciscan St. Joseph Hospital, Mancuso found herself increasingly drawn to the problem solving nature of medication safety. Following this experience, Mancuso pursued a PGY-2 residency in medication safety at Froedtert Hospital. Now as a practicing pharmacist, Mancuso finds her interests and involvements have only expanded. Not only does she continue to enjoy and grow her practice in medication safety and smart pump analytics, but Mancuso has also become active in advocating for a just culture and working to increase the visibility of second victim support services. The fulfilling nature of the work further motivates Mancuso to push for growth in these areas, especially as burnout in the healthcare profession persists.

Day to Day Practice

Given her role and multiple involvements, Mancuso collaborates with various providers, nursing leadership, students, and healthcare professionals on a daily basis. Whether she is at her site or working remotely, these interactions often involve reporting on new data or incidents within the workflow. Mancuso interacts the most with her colleagues in the information technology department and her end users. Mancuso primarily works with nursing leadership and nursing as her end users. As these individuals use the workflow on a daily basis to care for patients, clear, frequent, and timely feedback is crucial in building sustainable and efficient drug workflows. Her main goal is to break down these complex systems and "make it easy for these users to do the right thing." Beyond her daily responsibilities, Mancuso is also a co-chair for the Froedtert Hospital Medication Safety Committee and co-lead of the Pharmacy Society of Wisconsin's Medication Safety Collaborative.

Medication Safety

Mancuso would describe her practice as goal- and project-oriented. As the needs of end users, institutions, and patients evolve, so must the work focus. In this line of work, clear expectations must be set with special focus on increasing communication following events, preventing events, optimization of systems, and establishing areas of practice that are at the highest risk for errors. With equal emphasis placed on both prospective and retrospective analysis, Mancuso is confident her team can continue to meet expectations and be successful. Mancuso also cites that an institution that focuses on addressing errors within the system positively contributes to a just culture. What makes Mancuso's practice unique is the collaboration needed to build efficient workflows. Mancuso attributes the department's success to her outstanding colleagues. She describes her team as open-minded and committed. They consistently put forth a high level of involvement and collaboration. On top of the multiple trainings, Mancuso has recently become a Certified Professional in Patient Safety (CPPS). She also holds certifications in peer support, including mental health first aid. This training teaches participants how to address and de-escalate situations when an individual is in crisis. As more institutions recognize the importance of mental health and peer support in the context of second victim initiatives, Mancuso exemplifies the significant role pharmacists can play in expanding these programs and providing different avenues to improve outreach.

Bumps in the Road

The biggest challenge Mancuso faces when working on quality improvement projects is prioritizing which project is most important at the moment. One consideration is how the project plays in the current healthcare structure, such as thinking about when and where to move the quality improvement forward, and who should be involved in the process. To face this challenge, Mancuso has suggested a few components. Leadership teams are essential for helping with the implementation and leading to successful projects. Communication is another key to success. It is necessary to communicate with the primary stakeholders when implementing the project to consider different perspectives.

When implementing a project, one concern Mancuso used to have was the fear of failure. She overcame this by setting realistic expectations and collaborating with both leadership and key stakeholders. Nevertheless, fears should not stop us from brainstorming new quality improvement projects. The main driving forces for Mancuso to practice advancement and quality improvement are current data and event prevention/review. Mancuso gathers quality improvement data, including a medication safety scorecard, to search for gaps within the system and opportunities to address the issues.

Future Plans

Growth and opportunities are available at organizational and national levels in the business aspect of pharmacy. Within her organization, one opportunity that Mancuso seizes is safety in medication administration through the use of technology, such as barcode administration and interoperability. One newer area for growth is second victim support. After traumatic events in patients, many healthcare providers are "second victims," who experience both emotional and physical symptoms associated with the events, and it is incredibly valuable to

talk to peers who have similar experiences. Mancuso is actively involved with the Support Our Staff (SOS) program by providing peer support for second victims and structuring a second victim resilience and burnout page on the organization's intranet to help support staff.

On a state level, Mancuso is the co-lead of the PSW Medication Safety Collaborative, which is also a great way for interested individuals to join and connect with pharmacists within the field to learn more about medication safety issues.

On a national level, Mancuso is an active member and collaborator on the Vizient Pharmacy Quality, Safety and Compliance Committee.

Advice for Getting Involved in Pharmacy Businesses

Implementing medication safety advancement initiatives from scratch can be challenging, but persistence and collaboration are the keys to success. Mancuso suggests coming up with a written proposal to help organize your thoughts and set the intentions of the project. Collaboration with other pharmacists who have similar, established interventions is also a great way to start getting involved and learning about the processes.

For people interested in getting involved in the business side of pharmacy, connecting and shadowing are great opportunities to learn about the pathway. For instance, PSW's Medication Safety Collaborative will be a window to learn about project initiation and management, providing an experience to preview pharmacy businesses in action.

Caroline Paley is a 2024 Doctor of Pharmacy Candidate and Charisse Yan is a 2025 Doctor of Pharmacy Candidate at the University of Wisconsin-Madison School of Pharmacy in Madison, WI.

Spotlight Writing Club

ROSALIND FRANKLIN UNIVERSITY OF MEDICINE AND SCIENCE STUDENT WRITING CLUB:

Business Member Spotlight: Jessica Moschea

by Clifton Eboweme, 2024 PharmD Candidate, Susan Smock, 2024 PharmD Candidate

Jessica Moschea, PharmD, is the director of pharmacy services at Aurora Medical Center-Bay Area in Marinette, Wisconsin. Her pharmacy education was completed at the University of Wisconsin–Madison, and she received her Doctor of Pharmacy degree in 2013. She stumbled upon the opportunity for a career in healthcare administration during her rotation at the Pharmacy Society of Wisconsin (PSW). Moschea's passion for projects that enhance pharmacist training and help patients led her into a conversation at a PSW executive board dinner that changed her life. This eventually led Moschea into her search for a healthcare administration residency. She went on to complete both PGY1 and PGY2 residencies in healthcare administration at Aurora Health Care. In her current position, she gives back to the profession by serving as the Region D director on the PSW Board, as a member of the PSW Health System Advisory Committee, and on the Diversity, Equity, and Inclusion (DEI) Taskforce.

Day to Day Practice

At a smaller, non-24-hour hospital, pharmacists have unique opportunities to sharpen their skills. Teammates have the opportunity to gain expertise in all areas of hospital operations, enabling them to become versatile and knowledgeable in multiple roles. In her role as a director, Moschea offers extensive support to her team, including opportunities for pharmacy technicians to conduct medication histories. The importance of creating a learning environment was instilled in Moschea during her residency years, and she makes it a priority to implement all system recommendations at her site. Moschea's belief in promoting ongoing learning and development for all teammates, including both technicians and pharmacists, is a testament to her commitment to fostering a culture of professional growth and excellence. This empowers pharmacy technicians to maximize their capabilities and expand their potential. Moschea firmly believes in promoting ongoing learning and development for all staff members, regardless of whether they are a technician

or a pharmacist.

As COVID-19 cases peaked, Moschea took it upon herself to explore avenues to assist other healthcare professionals and look for ways to alleviate stress and maintain a positive working environment. She prioritized taking care of her team so they could care for patients. Moschea actively listened to her team's suggestions to ensure pharmacy operations were not disrupted. The team implemented "flex shifts" as a unique solution to address the need for extra help during busy days or in specific areas of the pharmacy. With this approach, a technician or a pharmacist on a flex shift assumed the role and fulfilled responsibilities requiring additional assistance, preventing overburdening of colleagues and ensuring a smooth workflow.

Raising the Bar

Moschea is a leader at Advocate Health in DEI. She serves as co-chair of a market, interdisciplinary inclusion council and is the chair of the pharmacy DEI team. She is currently spearheading a project on DEI, aiming to create an inclusive environment for all teammates. She emphasizes the importance of seizing opportunities with her team and readily accepts the responsibility to set DEI goals for the pharmacy enterprise as a way to bring about positive change. She demonstrates a commitment to creating a more inclusive and equitable workplace for all teammates, as well as promoting a culture of respect and understanding, which is essential for building a diverse and inclusive team. By recognizing the importance of addressing unconscious biases, she is paving the way for positive change in the hospital and beyond. Moschea's plans to incorporate DEI on a small and large scale are commendable, as the enterprise aims to raise awareness, promote education, and encourage difficult conversations about diversity, equity, and inclusion in the workplace. Incorporating videos, book clubs, and training on DEI can help to promote understanding and empathy among teammates, and provide valuable insights into the experiences of underrepresented groups. By encouraging teammates to engage in these activities, Moschea is advancing a culture of continuous learning and growth and helping build a foundation for greater DEI awareness and understanding.

Moving Forward

Moschea's approach to work and life serves as an inspiring example for everyone to follow. It is important to prioritize our own well-being, maintain a healthy work-life balance, and not let our jobs define who we are. By taking a step back and focusing on self-care, we can be more effective in our roles and help others. Additionally, having a sense of self beyond our professional titles helps to provide a sense of resilience and flexibility, allowing us to navigate setbacks and challenges more effectively. Moschea's lessons are particularly relevant in the context of the pandemic, where many people struggled to find balance between their work and personal lives. By following her example, her colleagues can lead happier, more fulfilling lives and be more effective in helping others in the workplace.

Moschea's dedication to patient care and her innovative approach to pharmacy management make her an invaluable member of the Advocate Health team. Her commitment to excellence has helped ensure that patients receive the highest quality of care possible.

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