Summit on the Future Treatments in Hemophilia

Findings from the AMCP Market Insights Program

Meeting Objective

- Collect insights to help payers manage access and product utilization amidst the introduction of new hemophilia treatments
- Defining the role of factor, emicizumab and future therapies in patient outcomes
- Understand changing business models for care management as non-factor replacement product use increases
- Collect and disseminate best practices for evaluating hemophilia outcomes and value of specific therapies and interventions

Introduction

Hemophilia is an X chromosome-linked genetic disorder that arises from missing or defective factor VIII (hemophilia A) or IX (hemophilia B). Hemophilia A occurs in 1 in 5,000 live male births and is about four times as common as hemophilia B. The number of people with hemophilia in the United States is estimated to be about 20,000 individuals.[1] Although it is a rare condition, the costs of hemophilia treatment are an important consideration for payers and employers. Hemophilia is among the top ten therapeutic categories for pharmacy spending in the United States, and is the fifth most expensive specialty condition for medical benefit spending.[2] Patients with hemophilia experience bleeding following an injury and may also have spontaneous bleeding episodes, often into their joints and muscles leading to substantial disability. To reduce the risk of bleeding, patients with hemophilia typically administer factor concentrate intravenously multiple times per week. The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia.

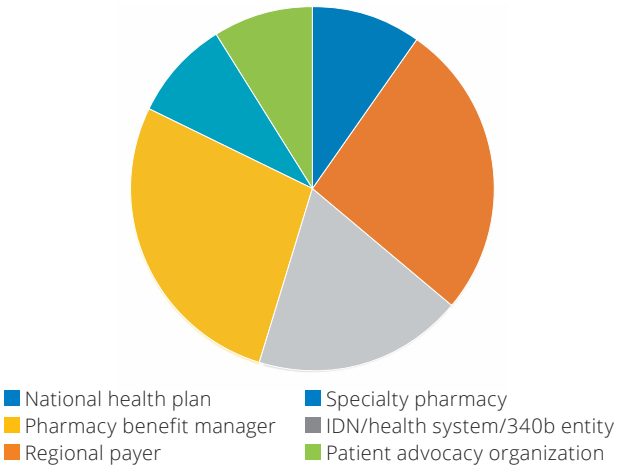
Hemophilia is categorized as mild, moderate, or severe, based on symptoms, including clotting factor blood levels. Severe hemophilia, in which patients have factor levels less than 1%, affects approximately 60% of patients, moderate hemophilia (factor levels 1% to 5%) affects approximately 15%, and mild (factor levels > 5% to 49%) affects the remaining 25%.[1,3]

Concentrated factor VIII replacement, often referred to as clotting factor or factor, is the cornerstone of hemophilia A treatment. Plasma-derived factor from human donors is one treatment option, although approximately 75% of patients with hemophilia use factor that is derived from recombinant DNA technology.[1]

Although factor replacement therapies are effective, they are associated with treatment burdens, including intravenous administration, the frequency of infusions, and the risk of developing neutralizing antibodies, or inhibitors, against replacement factors. However, the treatment pipeline shows the promise of alternative coagulation promoters (ACPs), such as gene therapies, anti-tissue factor pathway inhibitor (TFPI) monoclonal antibodies, and antisense RNA interference oligonucleotides, to target areas of significant unmet need.

To address the increasing costs associated with treating patients with hemophilia, and in light of emerging treatment options for managing patients, AMCP convened an expert forum of stakeholders. Forum participants included representatives from regional and national health plans, integrated delivery networks, 340b entities, pharmacy benefit managers, specialty pharmacies, and patient advocacy organizations (Figure 1). Participants discussed the evolving role of factor, inhibitor management, the emergence of nonfactor treatments pipeline therapies (including gene therapy) and the impact of new treatments on the delivery of care.

Figure 1. Market Insights Forum Participant Mix



Evolving Role of Factor

Payers currently monitor the usage and spend for factor on a monthly, quarterly, and annual basis in their efforts to be good stewards of the health care dollar. However, there can be significant variability in month-to month factor use, which makes predicting short-term utilization of factor difficult. Several issues complicate the ability of payers to manage hemophilia treatment. As with many replacement treatments, factor dosing is individualized based on unique patient needs, including frequency of bleeds, and the importance of bleeding prevention. It can be difficult to predict the frequency and intensity of bleeds; even for a patient with mild hemophilia. Health plans therefore have low predictability in the overall usage of factor replacement therapies, and instead rely on looking at longer-term (e.g., annual) trends to assess changes in populations.

Joint bleeds can cause significant impact on patient quality of life. A single joint bleed can result in morphological changes within the joint space that affects future morbidity. Therefore, early and appropriate treatment of a bleeding episode is critical to minimize complications. The risk for micro bleeds resulting in joint damage is to be considered

"Dose optimization is getting [to] what's being prescribed versus dispensed and how you're appropriately dispensing that to the patient. There is a financial savings associated with doing something different related to frequency of dosing…So, had you not made that change, you would end up with wastage."

when assessing whether to initiate prophylaxis in patients with mild or moderate hemophilia. All patients with severe hemophilia are candidates for prophylactic treatment but not all receive it. Generally, prophylaxis is not initiated until after a severe complication, such as, a joint bleed, or intracranial hemorrhage.

Some hemophilia treatment centers (HTCs) collect and use drug pharmacokinetics to guide dose optimization and monitor efficacy after treatment changes. Some payers are interested in accessing this information to support coverage determinations and reduce the burdens of prior authorization programs. Payers are also beginning to link their pharmacy and medical claims data in order to assess the impact of various treatment approaches on the total cost of care; however, not all payers have the ability to perform these analyses.

Providers commonly use factor assay results (referred to as assay management) to monitor

"By the age of 25, 90% of those with severe hemophilia have chronic degenerative changes due to recurrent hemarthrosis in at least one joint."

hemophilia treatment, including monitoring variance in factor assays results to make dosing adjustments. Many patients self-administer factor at home, which also allows them to have product readily available in the event of a bleed, and to self-manage their prophylaxis. The amount of factor needed to manage a bleed varies between patients. In some cases, specialty pharmacies may auto-ship a certain amount of factor each month, which could result in an undesired accumulation of product in the patient's inventory. Additionally, early refills may be appropriate, especially after bleeding episodes.

"There's so much variance in care, it's hard to have management strategies."

Factor Inhibitor Management

Approximately one-quarter of patients with severe hemophilia A who receive factor VIII concentrates develop neutralizing antibodies known as "inhibitors." Inhibitor development is a serious complication of factor treatment and reduces the effectiveness of factor therapy. Inhibitors neutralize infused factor VIII, rendering it ineffective for prophylaxis (i.e., prevention) and on-demand treatment. The presence of inhibitors may increase mortality from hemophilia by increasing bleeding-related deaths. While it is not certain why inhibitors to factor occur, one trial, the SIPPET trial, found that recombinant products may be associated with a higher rate of inhibitor development than plasma-derived products.[4]

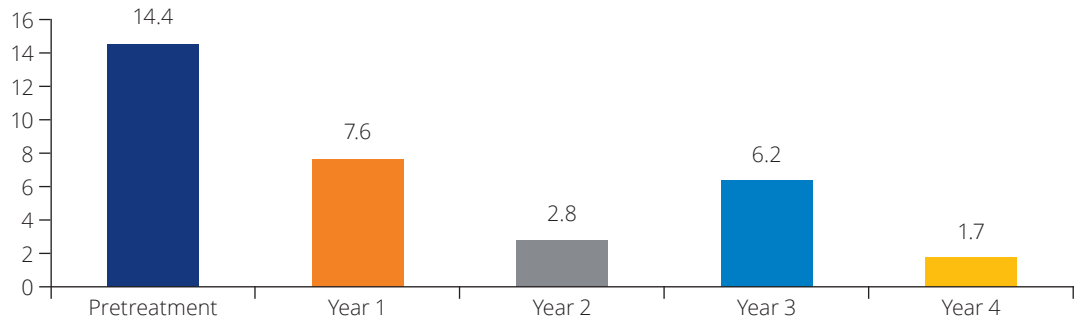
In some patients, inhibitors can be eradicated by inducing immune tolerance with high and then continual doses of factor VIII (immune tolerance induction [ITI]). ITI aims to permanently eradicate inhibitors and restore normal clinical responses to factor.[5] However, ITI is burdensome for patients, is costly, and is only effective at eliminating the inhibitor in 60% to 90% of treated patients.[6,7] These drawbacks limit the use of ITI. On the other hand, lifetime costs of treating patients with inhibitors is lower for ITI vs long-term treatment with bypassing agents, and ITI is associated with increased life expectancy.[8,9]

Patients with high levels of inhibitors to factor VIII who bleed are treated with "bypassing agents" (BPAs) such as activated prothrombin complex concentrate or recombinant activated factor VII. Even with BPA prophylaxis, many patients continue to have frequent episodes of bleeding. Suboptimal treatment for persons with inhibitors leads to greater disability, reduced quality of life, and higher morbidity and mortality.[10,11]

Emicizumab (Hemlibra) is a monoclonal antibody with dual targets ("bispecific") that allow it to bridge activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade. Emicizumab was approved by the U.S. Food and Drug Administration (FDA) in November 2017 as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII. In October 2018, it was approved for prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with or without factor VIII inhibitors.

Emicizumab is increasingly being used to avoid the development of inhibitors; however, there is limited guidance for payers around determining which patients are most appropriate for emicizumab. It has several potential benefits compared to factor, including subcutaneous injections and that its level of activity appears to be more constant than the varying activity seen as concentrations of factor VIII increase after an infusion and decrease prior to the next infusion. However, it does not eliminate the risk of a patient having a bleed. By offering another treatment option to ITI, emicizumab does shift the clinical decision-making option and process when determining whether to initiate ITI.

Figure 2. Annual Rate of Bleeding in Patients who Received AMT-60 Gene Therapy



Source: Leebeck[12]

"Emicizumab changes the question about whether to do immunotolerance therapy."

Some providers are initiating emicizumab in patients with highly active lifestyles who are at higher risk for bleeds, as well as to support patients in their efforts to remain physically active.

Payers have generally followed emicizumab's FDA approved package insert language for clinical coverage criteria in prior authorization programs. Existing coverage criteria for prior authorization programs for emicizumab focus on documentation that the patient has hemophilia, as well as information regarding factor use (prior, current or none), and, if they are receiving factor, why emicizumab should be added.

Real-world evidence (RWE) to inform and guide hemophilia treatment and outcomes is limited. Payers may focus on infusion logs, assay management, or inventory management, but few data are available regarding outcome-based analyses. Potential future assessments could address quality of life issues, including joint bleeds and psychosocial impact. However, it can be a challenge for payers to appropriately analyze sub-populations of patients due to data limitations around key disease specific characteristics, such as severity of hemophilia.

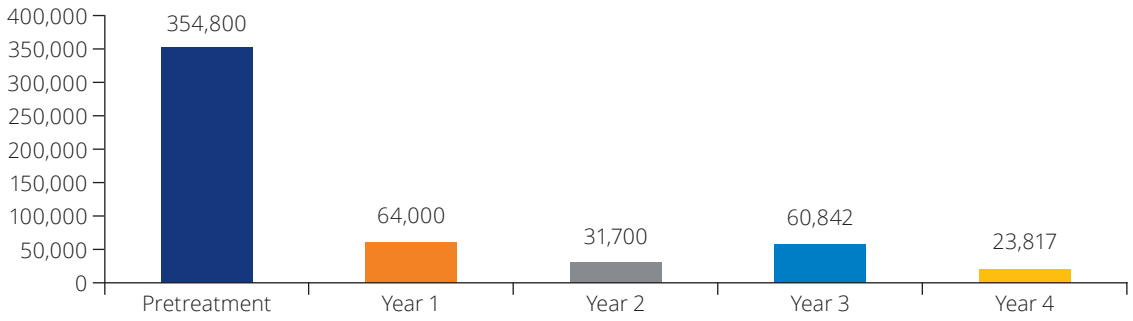
Development of more sophisticated systems for assessing RWE may inform future utilization management strategies for managing hemophilia. Some HTCs are collecting patient data and could collaborate with payers to share information that would inform payer policies. Additionally, digital tools are emerging as a potential strategy. Some programs have proprietary software for tracking outcomes that can be used for assessing dispensing history, monitoring bleed, and tracking patient reported outcomes (PROs).

Looking to the Future: Hemophilia Treatment Pipeline

Numerous treatments for hemophilia are in phase I, II, or III trials. Notably, fitusiran (ALN-AT3) is a subcutaneously-administered small interfering RNA (siRNA) therapeutic targeting antithrombin (AT) and potentially could be used to treat hemophilia A and B in patients with or without factor inhibitor. This agent is in phase III clinical trials and could receive approval as early as 2020 or 2021.

Concizumab, a high-affinity, humanized, anti–tissue factor (TF) pathway inhibitor (TFPI) monoclonal antibody, is in clinical development for the subcutaneous treatment of patients with hemophilia A, and hemophillia B with or without inhibitors. TFPI is a potent inhibitor of the coagulation

Figure 3. Annual Factor Consumption in Patients Who Received AMT-60 Gene Therapy



Source: Leebeck[12]

initiation phase. It also has promising results from early phase trials and is currently in phase III trials.

Numerous gene therapy products for the treatment of hemophilia are also in various stages of development and could be approved for treatment as early as 2020. Those likely to be approved first are intended for adult patients who have hemophilia B.

Gene therapy has the potential to transform the treatment of hemophilia. Patients who receive successful gene therapy treatment receive a single transfusion of a gene administered by a vector that results in steady, endogenous factor production. They experience the reduction or elimination of spontaneous bleeds and a reduction or elimination on of the dependence of patients on frequent infusions (Figure 2). Patients may need factor treatment in certain situations such as trauma or surgery since factor consumption is dramatically reduced, but not eliminated; (Figure 3). Currently, gene therapy has not been shown to reverse pre-existing joint damage.

Potential candidates for gene therapy include those who are currently receiving prophylaxis but are having difficulty optimizing treatment. Additionally, patient should be willing and able to participate in significant follow-up, as they may be at increased risk of undesirable and unpredictable outcomes which may present as delayed adverse event(s).

Because there are currently viable options for patient treatment, some patients, providers, and payers may take a wait and see approach to adopting gene therapy until more treatment options are available, and long-term data on treatment durability and safety are available. Continued rigorous disease management is necessary to minimize joint damage prior to initiation of gene therapy, and post-marketing surveillance will be paramount after presumed FDA approvals.

Potential Impact of Gene Therapy on Payers

The anticipated costs for gene therapy is in millions of dollars per patient, which may pose a significant burden for patients and payers. The impact of gene therapy on patient lifetime costs remains undetermined, as it is unknown if patients will need multiple infusions over time, and whether patients will develop antibodies that will preclude future gene therapy treatments.

The anticipated high investment in gene therapy, the impact of gene therapy on efficacy of other treatments, and the potential for patient migration between health plans, necessitates consideration of alternative payment models. Potential strategies include value-based arrangements such as outcomes-based agreements in which the

manufacturer assumes some of the risk for the outcomes associated with treatment. For example, the manufacturer could assume responsibility for the cost of any factor that is received within a defined time period after the patient receives gene therapy or the cost of treating a bleed.

Alternative payment models for gene therapy have also been proposed. Annuity payments, in which the costs associated with gene therapy is amortized over time, is one option. High-risk pools, or reinsurance programs, are another option. Many payers, including smaller plans and self-insured employers currently use reinsurance plans, also known as stop-loss carriers, to manage risks of high-cost patients.

The growing specialty market is placing burdens on reinsurance providers as reinsurance carriers have realized a significant increase in catastrophic claims, or those above $1M in recent years. Patients with claims of more than $1 million represented only 2% of the total number of stop-loss claims from 2014 to 2017, but roughly 20%, or nearly $600 million, of the total $3 billion in stop-loss reimbursement, and in 2018. Hemophilia resulted in $67.9 million in reinsurance claim reimbursements.[13] It is also important to recognize that reinsurance providers utilize several techniques, including those that limit access for patients to minimize risk. The eventual choice of an alternative payment model will ultimately depend on individual health plan environment and characteristics.

Impacts on Delivery of Care

Available data indicate that patients receive the best treatment when they are cared for by a primary hematologist and at a hemophilia treatment center (HTC). HTCs provide a comprehensive care model that addresses a wide range of clinical needs for patients (Figure 4). A study of 3000 people with hemophilia found that patients seen at an HTC were 40% less likely to die of a hemophilia-related complication and 40% less likely to be hospitalized for bleeding complications.[14,15]

HTCs receive a substantial portion of their funding through their participation in the 340b program for factor and are not directly reimbursed for many of the patient care services that they provide. As treatments for patients with hemophilia shift from factor usage to emicizumab, HTCs may see further financial impacts and need to consider new models for providing care and receiving reimbursement in order to continue to provide high quality care.

"What's the role of all of the different players, and how does that change with this moving into the gene therapy realm?"

Several issues must be considered as health plan stakeholders prepare to manage patient needs in an evolving treatment paradigm:

- **Treatment Access and Quality:** Anticipate hemophilia care in network and medical management strategies, to ensure access to specialized medical and pharmacy providers and support appropriate care as revenue streams shift.
- **Care Management:** Consider how best to coordinate multi-disciplinary outpatient and home-based services for members with hemophilia, determine what oversight and additional care coordination are needed and clearly designate accountability.
- **Affordability:** Consider pricing and cost-effective approaches for treatments of hemophilia, while allowing for individualized patient treatment plans.
- **Pharmacy Management:** Evaluate the full spectrum of services required to manage hemophilia, and contract with the most appropriate pharmacy to provide cost-effective and timely treatment services for routine and emergency needs.

- **Risk Adjustment and Risk Management:** Plans may need to work with the advocacy community and states to anticipate enrollment of members with hemophilia. These stakeholders can proactively recommend financing solutions to ensure member access to appropriate care; this may include risk adjustment or carve outs to avoid risk selection adversely affecting plans and members.

Summary

Advances in the treatment of hemophilia have the potential to improve outcomes for patients. However, the affordability of hemophilia treatment represents a burden for payers and patients. Utilization management strategies are limited in hemophilia due to the need to individualize patient treatments and the variability in treatment based on disease specific factors. As new nonfactor treatments enter the market, up-to-date guidelines for treatment of hemophilia are needed to support appropriate management strategies by payers. Alternative payment models may become an important strategy for payers to collaborate with manufacturers to share risk.

Nonfactor treatments also have the potential to shift reimbursement away from HTCs, which could potentially affect the quality of care received by patients. New models of care may be necessary to ensure that patients receive high-quality comprehensive care in new treatment paradigms.

Disclosures

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How Will This Impact Your Current and Future Decisions?

When evaluating processes and procedures to optimize hemophilia treatment and costs, health plans may want to consider the following:

- How to work with specialty pharmacies and HTCs regarding care coordination as treatment options are shifting?
- How are self-insured employers responding to specialty costs in response to new therapies and gene therapy?
- How does utilization management of factor replacement need to shift to reflect the personalized care for each patient?
- How can factor assays be used to make better treatment decisions and/or support dose optimization?
- What technology or data sets are needed to manage the hemophilia category?
- How to utilize and analyze the data provided/available by specialty pharmacies and HTCs to manage the hemophilia category?