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EDITORIAL

Alternate Settings for Infusions in Inflammatory Bowel Disease Patients: Homing in on Optimal Care

Sasan Mosadeghi[1] · **Sasha Taleban**[1]

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The US Food and Drug Administration's approval of the tumor necrosis factor (TNF) antibody, infliximab, in 1998 revolutionized the treatment of inflammatory bowel disease (IBD). The introduction of multiple other biologic therapies for IBD over time and treatment strategies aimed at improving mucosal healing and quality-of-life outcomes has increased the proportion of IBD patients receiving these therapies, which in turn has favorably altered the natural history of the disease, with infusion therapy with infliximab and other biologics becoming a mainstay of IBD therapy. TNF antibodies such as infliximab are implicated in the 72.2% 3-year compounded increase in the US annual expenditures for therapies for inflammatory conditions [1]. Non-drug costs comprise a substantial portion of the total cost of outpatient hospital-based infliximab administration with IBD [2]. Alternate care settings (ACSs) were developed in an effort to reduce costs and increase patient convenience. Currently, the ACS infusion market is estimated to represent approximately $9–11 billion/year in US healthcare expenditures, serviced by over 1500 infusion pharmacy locations, a substantial portion of the infusion market [3]. Yet, little is known regarding the impact of ACS infusions on patients and healthcare costs.

Home infusion services work directly with healthcare providers to deliver parenteral medication in the home or at alternate sites [4]. A variety of organizations provide this service, including hospitals, community pharmacies, or home health agencies [4]. Notably, home infusion is recognized as a potential model for the delivery of high-quality and cost-effective care due to a consequent reduction in the demand for hospitalization, improved quality-of-life, and reduced costs [5].

✉ Sasha Taleban
staleban@deptofmed.arizona.edu

[1] Department of Gastroenterology and Hepatology, College of Medicine, University of Arizona, 1501 N. Campbell Avenue, PO Box 245028, Tucson, AZ 85724-5028, USA

The American Society of Health-Systems Pharmacists' guidelines describe the services that home or alternate site infusion service providers deliver, providing detailed guidance on successfully working with a home infusion service provider in continuing infusions that were initiated in a healthcare facility [4]. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) published recommendations and guidance for pediatric gastroenterologists, health systems, and insurance payers regarding home and office space infusions for biologic therapies in pediatric IBD populations [5]. This is an important report that highlights many central considerations that also apply to the management of adult IBD. Some logistical considerations include liability, administrative support and policies, and cost and remuneration [5]. It is the responsibility of the physician to discuss risks and benefits of therapy and to prescribe medications appropriately, whereas infusion centers are responsible for the appropriate delivery of these medications [5]. Also, since there is a concern that there will be higher deductibles compared with hospital-based infusions, efforts should be made to minimize transfer of costs from the payer to the patient [5].

With infusion-based therapies, there are multiple patient care considerations, including patient safety, establishing standards-of-care, and minimizing impact on time spent at work or school [5]. These concerns are more challenging in the face of nonexistent mandatory regulations for ACS infusions. Home or office-based infusions should be safely administered, related orders reliably executed, and there should be ability to recognize and respond to complications [5]. Safety concerns include appropriate management of infusion reactions by nursing staff. Moreover, appropriate support is needed in dealing with different levels of severity. Unfortunately, there can be a lack of or inconsistency in coverage by primary medical teams when an infusion reaction occurs [5]. Currently, few studies detail patient safety issues, even in the rheumatology literature, where infliximab is used for treatment of rheumatic conditions. In a low-risk

population of children with Crohn's disease, home infusions of infliximab were safe and cost-effective [6]. Nonetheless, while home infusions may permit patients to receive therapy in a comfortable setting and at convenient times when compared with hospital-based infusions, the location of infusions does not affect health-related quality-of-life scores in pediatric patients [7].

In this issue of *Digestive Diseases and Sciences*, Checkley et al. report on the incidence and management of infusion reactions to infliximab in ACSs [8]. In a retrospective chart review of 796 patients with IBD who received a combined 5581 infusions with one home infusion company, a total of 109 infusion reactions occurred in 62 patients, accounting for 2% of all reactions and 7.8% of all patients, respectively. As the authors emphasize, this is comparable to the 3% per-infusion reaction rate observed in patients with Crohn's disease [9]. The majority of these reactions were acute, consisting of any adverse event occurring during the infusion or within 24 h after the infusion and were mild or moderate, resolving with rate adjustments and/or medication. Only 0.3% of all infusions were incomplete due to infusion reactions, with an emergency room visit required in an even smaller percentage (0.1%) of all of the infusions. The authors concluded that infusion reactions were uncommon and mostly mild or moderate in severity; in a majority of cases, the infusion reaction resolved and the therapy was completed. Yet, 18.3% of the infusion reactions occurred during or after one of the first three induction doses, and only 13.2% of the patients received an induction dose during the study period. Importantly, infusion reactions occurred at a rate of 14.3% of patients in the induction group, more than twice the 6.8% occurrence in patients who received a maintenance dose. The severity of the infusion reaction during induction was not reported. Overall, per-infusion incidence of infusion reactions was not different between patients with Crohn's disease and ulcerative colitis, although women were more likely to experience infusion reactions than were men.

The strengths of the study include the large sample size and the limited variability due to utilization of data from one home infusion provider. As the authors acknowledge, the study was limited by possible selection bias since the majority of the patients were receiving maintenance therapy. Since infusion reaction rates are higher in the induction phase, a change in this demographic correlates with a change in the incidence of infusion reactions [6], a factor incorporated into the NASPGHAN report, which aptly recommends against initiating induction doses at home in children [5]. Also, sicker patients are less likely to be referred for treatment at an ACS. The depth of information collected by Checkley et al. was also limited since several important potential confounders that may impact the rate of infusion reactions were not stated, including concomitant immunosuppressant use, location and severity of disease, and the occurrence of previous infusion reaction [10]. Moreover, reports of infusion reactions were limited and overall outcomes were not reported. These factors potentially challenge the external validity of the study.

Furthermore, in this study, the prescribing physician determined the use of premedication and participated in the management of infusion reactions, which included prompt recognition and the initial treatment via rate adjustments and medications. To ensure safety, infusion centers should not initiate therapies unless there is physician oversight; consequently, ordering physicians should work closely with infusion centers to ensure that pre-infusion laboratory testing is obtained. Therefore, the physician is not just someone who prescribes the infusion and laboratory tests, but is also someone responsible for managing complications that might arise, raising an important question regarding liability. Since risks and benefits of infusion therapy are discussed between patients and physicians, the latter needs to have an understanding of the operations and delivery of the infusion center in order to ensure that the patient is fully informed, a task complicated by physicians who work with multiple companies. In the setting of a complication, the responsible liable party, either the infusion center or the ordering physician, is unclear, given the lack of legal precedent governing such cases. NASPGHAN recommends a plan to ensure shared liability.

The number of alternate care biologic infusion therapies will continue to expand [3]. This study addresses a knowledge gap regarding safety of biologic infusions in an ACS. Although there are multiple other considerations that need to be weighed prior to implementing and fully adopting the ACS-centric model of infusion therapy, this study addresses an important piece of that puzzle. Further studies are needed to fully elucidate patient safety and examine clinical outcomes, logistics, utility, liability, cost, and patient preferences.

Compliance with ethical standards

Conflict of interest S. Taleban has served on the advisory board for Janssen Pharmaceuticals.

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