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Implementable Strategies and Exploratory Considerations to Reduce Costs Associated with Anti-TNF Therapy in Inflammatory Bowel Disease

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Abstract

A health care system is needed where care is based on the best available evidence and is delivered reliably, efficiently, and less expensively (best care at lower cost). In gastroenterology, anti-tumor necrosis factor (anti-TNF) agents represent the most effective medical therapeutic option for patients with moderate-to-severe inflammatory bowel disease (IBD), but are very expensive and account for nearly a quarter of the cost of IBD care, representing a major area of present and future impact in direct health care costs. The ImproveCareNow Network, consisting of over 55 pediatric IBD centers, seeks ways to improve the value of care in IBD – curtailing unnecessary

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costs and promoting better health outcomes through systematic and incremental quality improvement initiatives. This report summarizes the key evidence to facilitate the cost-effective use of anti-TNF agents for patients with IBD. Our review outlines the scientific rationale for initiating cost-reducing measures in anti-TNF use and focuses on three implementable strategies and four exploratory considerations through practical clinical guidelines, as supported by existing evidence. Implementable strategies can be readily integrated into today's daily practice, while exploratory considerations can guide research to support future implementation.

INTRODUCTION

In its 2013 report, "Best Care at Lower Cost", the Institute of Medicine advocates for a health care system where care is based on the best available evidence and is delivered reliably, efficiently, and less expensively[1]. The Institute of Medicine has estimated that there are excess costs of $130 billion annually due to inefficiently delivered services, and an additional $210 billion due to unnecessary services. It also concludes that systematic, evidence-based process improvement methods applied in various industrial sectors to achieve often striking results in safety, quality, reliability, and value can be similarly transformative for health care, improving outcomes and lowering cost.

It has been estimated that claims paid for Crohn's disease average $24,175 per patient per year, and that 24% of those costs are for treatment with anti-tumor necrosis factor (anti-TNF) drugs, an amount approximating the cost of inpatient hospitalizations[2]. The anticipated 3-year compounded increase in annual spending in the United States for anti-TNF use in inflammatory conditions is 72.2%[3].

Anti-TNF agents, such as infliximab (Remicade™) [4,5,6,7,8], adalimumab (Humira™)[9,10,11,12,13,14] and certolizumab pegol (Cimzia™)[15,16], represent the most effective medical therapeutic option for patients with moderate-to-severe inflammatory bowel disease (IBD), either Crohn's disease (CD) or ulcerative colitis (UC). Recent trends in induction and maintenance therapies for CD and UC have focused on increasing anti-TNF use, with new biological agents receiving attention in published safety and efficacy multi-center clinical trials[17,18,19,20,21,22,23,24,25] or approval for treatment of IBD[26].

In light of increasing anti-TNF use, these drugs represent the primary focal point where gastroenterologists can lead the effort to control health care costs in IBD without compromising the quality of care or outcomes. Judicious and evidence-based use of anti-TNFs will continue to be a vital policy effort for the present and foreseeable future of IBD care. A recent editorial succinctly communicates the overarching message of this clinical review: value-conscious gastroenterologists can work together to optimize IBD care plans involving anti-TNFs[27].

Given these considerations, physician members of the ImproveCareNow Network formed the Reducing Cost Strategic Initiative for Biologic Therapies, and initially outlined all potential areas for cost-reduction. ImproveCareNow is a primarily US-based, growing multi-center pediatric IBD collaborative formed in 2007, currently consisting of over 55 pediatric care centers and representing more than 15,000 children and youth with CD and UC[28,29,30].

The aim of this review is to outline the best available evidence to initiate cost-reduction strategies within the standard-of-care models for anti-TNF use. Formative clinical reviews and editorials have already summarized the increasing evidence from original studies and described the scientific rationale for various clinical strategies associated with anti-TNF use[31,32,33,34,35]. However, no report exists to date to contextualize the practical clinical application of anti-TNF use within an organized effort to streamline direct health care costs and reduce over-utilization.

Within the framework of the published literature and our collective patient-care experience, the goal of this report is to answer the primary question: What are *implementable strategies* and *exploratory considerations* for cost-efficient anti-TNF use while maintaining the highest quality of IBD care? What is best care at lower cost? Implementable strategies represent recommendations with significant evidence to support cost-effective clinical practice. Exploratory considerations represent possible interventions based on emerging evidence for other cost-effective clinical practices.

IMPLEMENTABLE STRATEGIES

Implementable Strategy #1: Reduce costs of avoidable dose intensification or class switching by eliminating episodic anti-TNF use and improving patient education

Evidence suggests that long-term durability of anti-TNF effectiveness is associated with improved health outcomes[36,37]. Administering regularly scheduled anti-TNF infusions and eliminating episodic anti-TNF use are necessary to optimize its effectiveness. Meticulously scheduled anti-TNF maintenance therapy will curb over-utilization associated with unnecessary or preventable dose escalation or class switching. Such practice will improve patient outcomes[38,39], increase cost-effectiveness[40], enhance drug efficacy[41], reduce premature immunogenicity through auto-antibody formation, and decrease the probability of early drug tolerance[42,].

Studies show that failure to adhere to agreed-upon regimens contributes to worse health outcomes. Direct costs of IBD care from loss of response (LOR) to anti-TNF therapy may be more attributable to non-adherence than drug efficacy[43]. When the patient and gastroenterologist decide to implement anti-TNF therapy for the induction and remission of IBD, it is important to agree upon the therapeutic goal of sustainability, not rescue – to enhance the probabilities of long-term response of the initial anti-TNF therapy. It is not uncommon for patients and families to wish to prematurely withdraw from a successful anti-TNF regimen, especially among patients who have attained remission and good quality-of-life on biologics but are averse to the idea of prolonged or escalated drug therapy. Patients would benefit from an early introduction to and adoption of the evidence-based rationale against episodic anti-TNF therapy. Agreeing upon maintaining a long-term scheduled anti-TNF regimen after achieving clinical remission, or for at least 1 year after achieving complete mucosal healing, will improve outcomes, especially patients who are on self-injectable anti-TNF agents[44,45].

Implementable Strategy #2: Reduce over-utilization costs by accurately determining indication for escalating anti-TNF use

Evidence from a recent meta-analysis reports a 25% to 46% probability of concomitant irritable bowel syndrome (IBS) in IBD patients.[46] However, clinical signs and symptoms in patients with IBS and IBD are especially difficult to attribute to one or both diseases. For gastroenterologists, avoiding the use of anti-TNFs to treat patients with symptoms due to IBS is particularly important in reducing over-utilization and minimizing harm. A prospective, cross-sectional cohort study reports that the Crohn's disease activity index could not distinguish between IBS and CD patients[47]. Empiric dose escalation, increase in frequency, or class switching in patients with IBS and IBD without objectively determining systemic and/or mucosal inflammation will frequently lead to over-utilization. To avoid misuse or overuse, recommendations include: ruling out infectious causes (e.g., C. difficile infection), checking for serological markers for inflammation (i.e., C-reactive protein and complete blood count parameters), and measuring fecal calprotectin prior to initiating or adjusting anti-TNF regimens. Additionally, on a case-by-case basis, low- or non-ionizing radiologic studies (e.g., ultrasound and magnetic resonance enterography) and endoscopic index scoring (e.g., Crohn's disease endoscopic index score) can be utilized to clarify the clinical picture between IBS and IBD[48,49].

In specifically detecting sub-clinical inflammation in IBD patients with IBS-type symptoms, there is evidence for measurements of calprotectin as a biomarker for mucosal inflammation[50]. Determination of fecal calprotectin to assess mucosal status may not be cost-prohibitive, as Medicare reimbursement is $28 per assay in 2012,[51] although costs to private insurers may be higher. There are two systematic reviews and meta-analyses that highlight the potential for non-invasively detecting acute and chronic mucosal inflammation using calprotectin. The first meta-analysis pooled data from 13 studies, including 6 in adults and 7 in children and adolescents, and report a pooled sensitivity and specificity of 0.93 and 0.96 in adults and 0.92 and 0.76 in children[52]. The second meta-analysis reviewed 8 studies in pediatric cohorts and reported a pooled sensitivity and specificity of 0.978 and 0.682 for pediatric IBD[53]. A recent cost-effectiveness analysis shows that any value greater than 50 μg/g maximizes the sensitivity of calprotectin for mucosal inflammation and supports the utility of fecal calprotectin as a biomarker test when clinical suspicion alone for mucosal inflammation is ambiguous[54]. This is directly applicable in determining whether patients on anti-TNF therapies may need dose intensification. Future work is needed to determine whether there is any histopathologic difference or likelihood of mucosal healing based on specific calprotectin positivity thresholds (i.e., 50,100, or 200 μg/g).

Implementable Strategy #3: Reduce non-drug infliximab costs through shortened infusion times after initial safety is clearly established

Evidence suggests that non-drug costs associated with infliximab infusions are substantial. In the U.S., non-drug costs of infliximab administration for IBD may be greater than the actual drug costs in medical practices using hospital- or infusion center-based sites. One analysis reports that personnel costs required to administer the drug based 771 encounters for infliximab at a pediatric tertiary care center is 77% of the total health care cost for each infusion encounter[55]. Transparency of cost is difficult, and heterogeneity of charges to

reimbursements is likely; nonetheless, reducing non-drug costs is an opportunity to substantially reduce the cost of anti-TNF treatment.

Patient safety must precede considerations for cost-efficiency or convenience. Given this priority of "first-do-no-harm," the available evidence suggests that non-drug costs associated with infliximab administration can be safely reduced by abbreviating the typical 2- to 3-hour infusion period to ≤ 1-hour. A recent meta-analysis which included pediatric data when available concluded no increase in adverse reactions associated with the abbreviated infusion of infliximab[56]. In particular, when prior infusions have shown no adverse reactions on the standard 2- to 3-hour infusion period, patients undergoing shortened infusion times of infliximab under a carefully monitored medical care setting can reduce both future opportunity loss (e.g., time away from work or school) for the patient and/or family and direct healthcare costs. The current data for this strategy are more robust in adults than in children. Among the 13 original studies in the meta-analysis, 2 studies included adult and pediatric patients as young as 14 years of age while 1 pediatric study considered patients as young as 12 years of age. Currently, certain ImproveCareNow Network centers have been using 1-hour maintenance infliximab infusion protocols in acute care settings after patients safely undergo 3 initial infliximab doses at 2- to 3- hour infusions. Of note, infusions in a monitored acute care settings is still the current standard of care, although preliminary results for home infusions appear to be cost-efficient with high patient satisfaction[57]. However, at this time, there is insufficient evidence to support the safety of large scale home infusion programs, particularly in children.

EXPLORATORY CONSIDERATIONS

Exploratory Consideration #1: *Self-injectable anti-TNFs*

Since prospective comparative effectiveness research is limited between anti-TNF therapies[58], a formal head-to-head evaluation between infliximab and adalimumab for CD or UC when initiating anti-TNF therapy is not available – although retrospective analysis between the two drugs finds similar effectiveness in CD after 26 weeks of treatment[59]. In pediatrics, infliximab is the only anti-TNF that is FDA-approved in children, but off-label use of adalimumab is not uncommon. Clinicians and patients should make it a priority to discuss disease management expectations and logistical differences when starting on either infliximab or adalimumab, seeking to individually tailor the regimen to a patient's lifestyle and realistic estimation for long-term medication adherence. In our experience, self-injectable agents may have added risk of non-adherence leading to worse outcomes among adolescent IBD patients. The tradeoff between cost-savings and potential for worse outcomes due to non-adherence with self-injectable anti-TNFs is unknown. More clarity is needed regarding the difference in total direct costs between anti-TNF infusions and self-injectables.

Exploratory Consideration #2: *Combination therapy*

Immunomodulators, in the form of 6-mercaptopurine and its pro-drug azathioprine, are very cost-affordable drugs compared to anti-TNFs. Based on an azathioprine therapeutic dose of 100 mg per day, the annual drug cost would be less than $1500[60]. Although a formal cost-

effectiveness analysis is not yet available, the use of adjunct immunomodulators in combination with anti-TNF agents (i.e., combination therapy) are shown in randomized clinical trials to be more effective than anti-TNF monotherapy in efficiency and sustainability of clinical response. In CD, the SONIC trial for moderate-to-severe CD patients achieved significant incremental benefit with combination therapy over monotherapy (56.8% vs. 44.4% steroid-free remission) at week 26 for patients previously naïve to both agents[61]. Preliminary results show combination therapy to be superior to infliximab monotherapy in long-term outcomes in perianal fistulizing CD[62]. In UC, preliminary data from the SUCCESS trial duplicate the trends reported in CD. Combination therapy was superior to montherapy (40% vs. 22% steroid free remission) at week 16[63]. Although more longitudinal data are needed to understand long-term costs and benefits, extrapolation of direct costs of IBD health states in good versus poor control would validate combination therapy as a cost-saving measure. Also, a more precise estimate of additional risk of rare but serious events (e.g., lymphoma) is important for patients on combination therapy.

Exploratory Consideration #3: Monitoring of anti-TNF drug levels and auto-antibodies

Gastroenterologists now have the option to monitor infliximab and adalimumab drug levels and auto-antibodies through commercial assays with a high-degree of accuracy and precision[64,65]. Cost-effective clinical care using an individualized anti-TNF dosing strategy depends on the usefulness of these tests, clinician interpretation of the results, and the baseline cost of the laboratory assays. To determine the etiology for LOR, a clinician is faced with interpreting whether one or a combination of drug levels and auto-antibodies suggests anti-drug antibody, immune complex formations[66,67] or patient-specific accelerated drug clearance[68] to determine the etiology for LOR. One randomized, controlled, single-blind multi-center study of 69 patients showed that individualized infliximab therapy based on drug levels and auto-antibody titers results in similar clinical response rates and lower treatment costs compared to the dose intensification strategy[69]. A formal cost-effectiveness analysis in CD patients corroborates this trial. Although remission rates were similar over a 1 year period, a testing-based strategy cost $6,000 less than the empiric dose escalation strategy among patients with secondary LOR[70]. A weakness in this analysis includes missing the true cost of drug level testing, because out-of-pocket costs to the patients were not considered along with a higher cost of drug level testing[71]. At present, less cost-prohibitive drug level and auto-antibody testing for anti-TNF agents are entering the market, which may provide gastroenterologists more options in the near future. In the meantime, gastroenterologists should carefully weigh individual benefits and costs to patients and families.

Exploratory Consideration #4: Complete mucosal healing as a clinical endpoint

The evolving thought is that complete mucosal healing should be considered the major therapeutic goal in IBD, especially in UC[72,73,74]. Complete mucosal healing refers to the absence of mucosal breakdown and ulcerations on endoscopic assessment[75]. The working hypothesis is that disease management with early and aggressive anti-TNF use can modify the future disease course by maintaining complete mucosal healing, as described in the literature by the phrase “deep remission”[76,77,78]. Complete mucosal healing is now

considered a primary clinical endpoint in newer randomized trials – such as in the EXTEND (Extend the safety and efficacy of adalimumab through endoscopic healing) study[79]. In this trial using adalimumab, complete mucosal healing was evaluated by ileocolonoscopy, and investigators found that 15/62 patients achieved this endpoint at weeks 12 and 52. Although the application of complete mucosal healing in clinical practice is not yet known, the implications on cost-effective use of anti-TNF agents are important to discuss. For example, if achievement of present-day complete mucosal healing renders a relapsing and remitting IBD form to be more manageable and less aggressive in the future, this consideration has the potential for major cost-benefit impact. While additional costs may be required up front for more aggressive use of anti-TNF agents and more frequent endoscopic evaluations, especially soon after diagnosis, the overall cost-savings may result later from averted future healthcare use. At this time, considering this lifetime perspective is difficult because more data about the significance of complete mucosal healing are required to make formal recommendations.

CONCLUSION

Gastroenterologists have an opportunity to play a leading role in providing the best care at lower cost for patients with IBD by administering anti-TNFs with an evidence-based approach that is more efficient and eliminates unnecessary services. In today's era of biologics for the management of IBD, we recommend that the 3 implementable strategies we describe be introduced into real-world practice, particularly in a setting such as a quality improvement network or a closed healthcare system where the impact of such strategies on outcomes as well as cost can be measured and evaluated. We also present 4 emerging exploratory considerations with growing evidence for future cost-efficiency. Although not an exhaustive review on potential ways for improving cost-effectiveness of anti-TNF therapy, this report focuses on the key evidence-based and practical ways to increase cost-efficiency and decrease cost-burden associated with anti-TNF use. We acknowledge the substantial variability in real-life use of anti-TNF agents without a clear consensus among gastroenterologists (e.g., differences between pediatric and adult IBD states, precise estimates of increased risk for lymphoma or infections when aggressively immune suppressed)[80].

Finally, since their real-life application is uncertain[81], we did not elaborate on the developing area of "biosimilars." However, biosimilars are well-positioned to be a disruptive force in European, Asian, and U.S. markets, competing directly with current biologic agents[82]. Developmental stages of various biosimilars range from Phase 1 to completed Phase 3 trials[83], and early efficacy results are promising and may rival mainstream anti-TNF agents[84]. The latest cost-savings forecast is $250 billion dollars over a 10 year span in the U.S. if 11 biosimilars are approved to compete with current brands of biologic agents used across all diseases[85]. Most recently, Inflecta – a biosimilar version of infliximab – has been approved for use in Europe by the European Medicines Agency. Projected FDA-approval for use in the U.S. is possible as early as 2015[86].

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Abbreviations

TNF	tumor necrosis factor alpha
IBD	inflammatory bowel disease
CD	Crohn's disease
UC	ulcerative colitis
FDA	Food and Drug Administration
LOR	loss of response

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