The cost and benefit of anti-TNF therapy from a population perspective—for what it's worth

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Anti-tumor necrosis factor therapy (anti-TNF) has dramatically changed the treatment of both Crohn's disease (CD) and ulcerative colitis (UC). The efficacy of this class of therapy has been established since the late 1990s when infliximab was shown to be effective in the treatment of moderate to severe CD and later fistulizing CD and UC (1-4). Since this time, additional anti-TNF agents have demonstrated efficacy in moderate to severe inflammatory bowel disease (IBD), including adalimumab (5,6) for both CD and UC and golimumab (7,8) for UC. In addition, several studies have further demonstrated the long-term efficacy of these agents based on both randomized controlled trials (RCT) and real-world data (9-11). While anti-TNF therapy has offered an effective treatment option for both CD and UC, the associated high costs of using these agents is often considered a drawback from a population standpoint. Several studies have demonstrated that the increased cost associated with using anti-TNF therapy has now surpassed hospitalization and surgery as the highest healthcare expenditure in patients with IBD (12-14).

With the costs associated with using anti-TNF, it is intuitively important to ensure the resultant benefit from a standpoint of long-term treatment outcomes, such as hospitalizations and surgery. However, the data on this is conflicting. A follow-up study of A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn's Disease (ACCENT) II showed significant reduction in hospitalizations (11% vs. 31%, P<0.05) and surgeries and procedures (65 vs. 126, P<0.05) with patients who received infliximab 5 mg/kg every 8 weeks (15). Similarly, a follow-up study from the Active Ulcerative Colitis Trial (ACT)-1 and ACT-2 showed significantly reduced colectomy rates after 54 weeks of treatment with infliximab (10% vs. 17%, P=0.02) (16). Lastly, a follow-up of The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) showed reduced risks of hospitalization (HR 0.42, P<0.05) and CD-related surgeries (0.6% vs. 3.8%; P<0.05) (17). While these follow-up studies from RCTs showed a clear benefit of anti-TNF in reducing hospitalizations and surgery, population-based studies have not shown such promising results. One study using data from a register-based observational cohort in Sweden showed that there was no difference in bowel resection rates in patients who continued anti-TNF therapy beyond 12 months compared to patients who discontinued prior to 12 months (18). Another study from the US evaluated claims data in UC patients and showed that over 50% of patients initiating infliximab, adalimumab, and golimumab remained on steroids after 12 months of treatment (19).

Most recently, a well-done population-based study from Ontario, Canada by Murthy et al. published in Gut showed that anti-TNF therapy has not led to expected declines...
in rates of hospitalization and intestinal resection (20). This study evaluated adult patients with CD and UC living in Ontario, Canada between 1995 and 2012 using an administrative claims database. This database is considered effective for capturing true population-level data and trends since Ontario uses a single payer system with 100% coverage for medically necessary services and occasionally subsidized coverage for select expensive drugs, such as biologic therapies. The study utilized an interrupted time series design where trends 6 years prior to the introduction of infliximab were compared to trends after the introduction of infliximab into the Canadian marketplace. Overall, the results showed that there was no significant change in expected hospitalization rates for CD (OR 0.1.06, 95% CI: 0.811–1.39) or UC (OR 1.22, 95% CI: 1.07–1.39). There was also no significant change in expected intestinal resection rates for patients with CD (OR 1.10, 95% CI: 0.810–1.50) or in colectomy rates for patients with UC (OR 0.933, 95% CI: 0.540–1.61). However, there was a decline in hospitalizations for UC in the small subgroup of patients who received publicly funded infliximab (OR 0.515, 95% CI: 0.342–0.777).

While these results may seem surprising, it is important to note a few reasons why the results of this study should be interpreted with caution. First, even though the design of this interrupted time study is unlikely to be impacted by other competing factors, there is a lack of detailed clinical data to determine the effect of confounding patient variables. Disease severity, one such potential confounding factor in similar population-based studies, and the impact of disease severity on the results of this study cannot be assessed. This is especially true for the CD population where there was strong penetration of infliximab into the marketplace as evidenced by a threefold increase in expected drug costs after marketplace introduction (OR 2.98, 95% CI: 2.29–3.86). Therefore, it is plausible that patients with more severe CD were being treated with infliximab, and this may have impacted treatment outcomes. Also, because publicly-funded infliximab patients were required to first demonstrate failure to conventional therapy, it is also reasonable to believe that some patients were being treated later in the disease course when the efficacy of anti-TNF therapy may be limited. This is supported by the pivotal studies on anti-TNF therapy that demonstrated higher clinical remission rates in the studies where participants had a shorter disease duration (2,6,21-23). On the other hand, the cost trends for patients with UC were different, highlighting another limitation in interpreting this study. Unlike for CD, the marketplace penetration of infliximab for patients with UC appeared to be low based on the lack of significant change in drug cost after introduction of the drug (OR 1.06, 95% CI: 0.955–1.18). Therefore, it is plausible that low drug usage in patients with UC was a primary factor that accounted for the lack of overall improvement in trends for hospitalization and surgery. Similarly, there may have not been enough time in the marketplace for the beneficial effects of UC to be demonstrated at a population-based level.

While the limitations in the study by Murthy et al. and its design are well-acknowledged by the authors, there are several other potential explanations for why there was a lack of decline in hospitalizations and surgery that pertain to treatment paradigms on when and how infliximab was used. The timing of infliximab initiation in relation to a patient’s disease course is important. It has been demonstrated that there is likely a “therapeutic window” for biologic therapy when initiation of therapy early in the disease course may prevent disease-related complications, such as stricture, fistula/abscess, and surgery (24). Also, a “top-down” approach to therapy demonstrated benefit in a landmark RCT by D’Haens et al. (21), favoring early biologic usage prior to treatment with conventional therapy. Similarly, a post-hoc analysis of the CHARM trial showed that there was likely a benefit to treatment early in the disease course (25). In this analysis, patients with IBD were required to fail conventional therapy prior to anti-TNF use. This factor may account for the lack of improvement in hospitalizations and surgeries. This notion is further supported by a recent population-based pediatric study, also from Canada, that showed that a parallel relationship between early usage of anti-TNF therapy and reduction in corticosteroid dose (26).

Furthermore, another factor that may account for why there was a perceived lack of benefit with infliximab usage at a population level pertains to how infliximab was used. Even though infliximab has been available for 20 years, the treatment paradigms for infliximab and other biologic therapies have evolved, and in fact, are still evolving. The timing of anti-TNF discontinuation (i.e., definition of treatment “failure” and lack of optimization), the role of concomitant immunomodulator use, goals of therapy, and the role of therapeutic drug monitoring (TDM) have changed greatly since infliximab was first introduced into the marketplace. Additional real-world population-based studies have shown that there is a high rate of discontinuation and non-persistence of biologic therapies among patients with CD and UC (27,28). Based on this observation and the lack
of a standardized definition of treatment failure, early anti-TNF discontinuation (i.e., lack of dose optimization) may be another factor that helps account for the absence of a population-level benefit for anti-TNF therapy. Also, the benefit of combination therapy with an immunomodulator has been demonstrated in both CD and UC by The Study of Biologic and Immunomodulator Naïve Patients in Crohn’s Disease (SONIC) and UC-SUCCESS Trials, respectively. In addition, two population-based studies have shown that early combination therapy with an immunomodulator may lead to biologic drug persistence and increased effectiveness. However, in the present study by Murthy et al., the penetration of concomitant immunomodulator use and its impact on disease outcomes at the population level are unknown. Therefore, underuse of combination therapy may have contributed to the observed lack of benefit from anti-TNF therapy. Furthermore, goals of therapy are changing with increasing evidence to support the objective outcomes including mucosal healing. Several studies have demonstrated the benefit of mucosal healing on long-term outcomes. Most recently, Yzet et al. showed that complete mucosal healing with a Crohn’s disease endoscopic index score (CDEIS) of 0 led to lower rates of treatment failure (25% vs. 48%, P=0.045), intestinal resection (0% vs. 11%, P=0.031), and CD-related hospitalizations (3.5% vs. 18%, P=0.013) over a median follow-up period of 4.8 years. From a population perspective, it is difficult to know whether the mucosal healing as a treatment target had been widely utilized and accepted, but based on the time period of this study, it is unlikely. This provides another plausible explanation for why there has been no observed benefit for anti-TNF therapy from a population-based perspective. Lastly, and perhaps most importantly, the beneficial role of proactive TDM is becoming increasingly demonstrated and recognized. A recent well-designed RCT by Assa et al. showed improved corticosteroid-free clinical remission from week 8 to week 72 (82% vs. 48%, P=0.002) in pediatric patients with CD who underwent proactive TDM compared with reactive TDM. Also, a previous retrospective study of 264 patients with CD (n=167) and UC (n=97) from multiple centers showed less treatment failure (HR 0.16, 95% CI 0.09–0.27), fewer IBD-related surgeries (HR 0.30, 95% CI: 0.07–0.33), less antibodies to infliximab (HR 0.25, 95% CI: 0.07–0.84), and fewer serious infusion reactions (HR 0.17, 95% CI: 0.04–0.78) in patients treated with proactive vs. reactive TDM of infliximab. With this said, the use of proactive TDM at a population level is unknown, and it is plausible that increased uptake of this beneficial practice would finally allow us to see a population-based benefit of anti-TNF.

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Footnote

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