Shooting for the Stars: Review of the STARDUST Trial and the Treat-to-Target Approach for Crohn's Disease

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Abstract: Crohn's disease (CD) and ulcerative colitis, collectively termed inflammatory bowel disease, are progressive autoimmune conditions of the gastrointestinal tract. Mucosal healing has been associated with fewer major abdominal surgeries and hospitalizations in patients with CD compared with patients with CD but without mucosal healing. Therefore, a treat-to-target (T2T) management approach to escalate treatment by targeting objective markers of inflammation rather than clinical symptoms alone has been introduced in recent years. The STARDUST trial is the first T2T randomized trial of adult patients with CD using endoscopy and biomarkers for dose adjustment of ustekinumab. Patients with active CD were randomized to 2 arms: T2T and standard of care (SoC). In the T2T arm, changes in dosing interval were based on endoscopic severity, clinical symptoms, and biomarkers, whereas in the SoC arm, dosing adjustments were made based on clinical symptoms alone. The primary endpoint was 50% or greater improvement in Simple Endoscopic Score for Crohn's Disease at week 48. The results of the primary endpoint found increased endoscopic response in the T2T arm compared with the SoC arm. However, the endpoint was not statistically significant using nonresponder imputation analyses. This article discusses the details and limitations of the STARDUST trial and addresses further questions regarding T2T approaches for CD.

Keywords
Crohn's disease, inflammatory bowel disease, treat-to-target, ustekinumab, mucosal healing, biomarkers

Crohn's disease (CD) and ulcerative colitis, collectively termed inflammatory bowel disease (IBD), are progressive autoimmune conditions of the gastrointestinal tract. They can lead to serious complications and disability over time, including hospitalizations, surgeries, and colorectal cancer.[1] The conventional approach to treating these conditions has focused on symptom control with escalation of therapy and/or surgery as symptoms worsen or complications develop. Numerous treatment options exist for these conditions and include 5-aminosalicylic acid, glucocorticoids, immunomodulators, biologics,

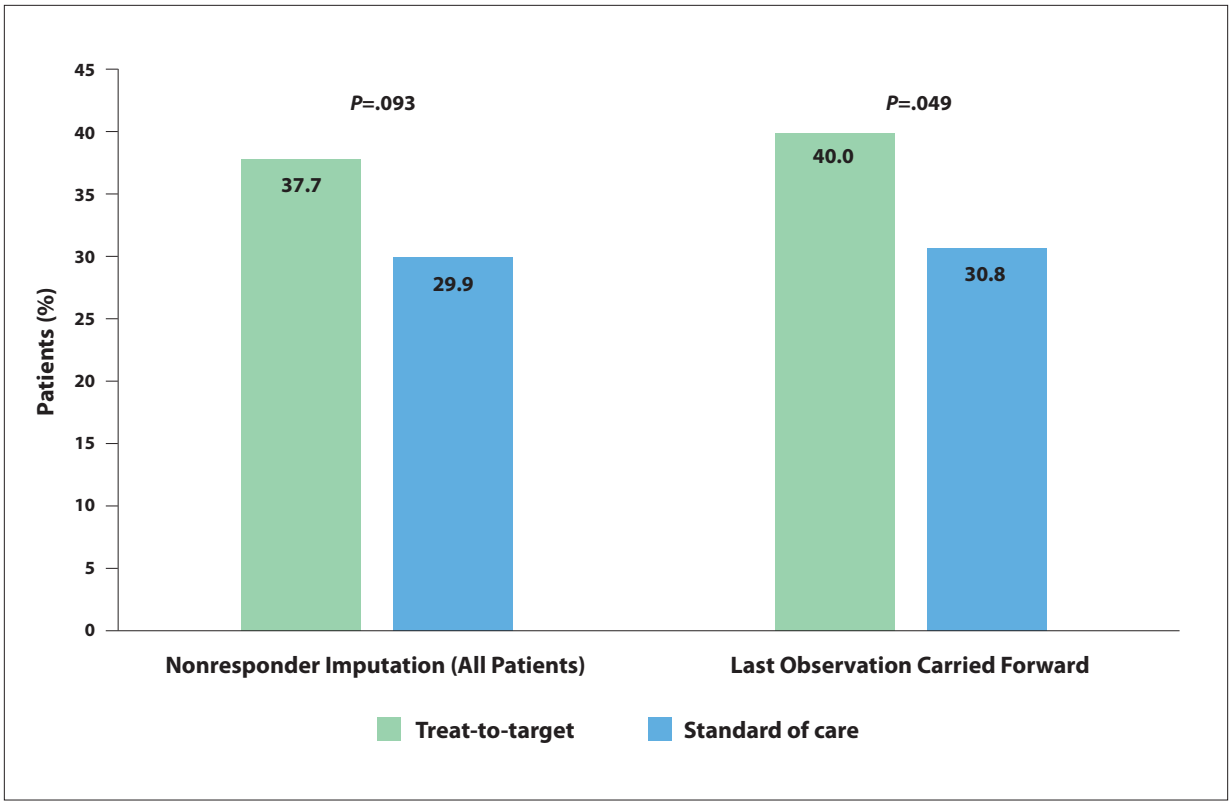

Figure. Primary endpoint of endoscopic response at 48 weeks comparing treat-to-target and standard of care.

and small molecules. Biologics include tumor necrosis factor–α inhibitors, anti-integrins, and anti–interleukin 12/23 agents. Small molecules include Janus kinase inhibitors and ozanimod (Zeposia, Bristol Myers Squibb). Increasing evidence has shown the importance not only of symptom control but of treating inflammatory lesions of these disorders to reduce later complications. In early-stage CD, Baert and colleagues showed that mucosal healing was associated with significantly higher corticosteroid-free remission rates 4 years after initiation of therapy.[2] Partial or complete mucosal healing has also been associated with fewer major abdominal surgeries and hospitalizations in patients with CD compared with patients with CD but without mucosal healing.[3]

Given the importance of mucosal healing and endoscopic remission in the disease trajectory of IBD, a treat-to-target (T2T) management approach has been introduced in recent years with the goals of minimizing disease activity, limiting progression, and ultimately improving long-term outcomes.[4] Studies have shown that T2T may impact disease progression and improve outcomes in IBD[2-4]; however, few prospective studies exist, and long-term data are lacking. The STARDUST trial was the first randomized trial of adult patients with CD using endoscopy and biomarkers for a T2T approach of dose adjustment of ustekinumab (Stelara, Janssen). This article reviews the details and limitations of the STARDUST trial and discusses further questions regarding T2T approaches for CD.

Study Summary

The STARDUST trial was a randomized controlled trial of adults with CD evaluating T2T using early endoscopy, serial biomarkers, and clinical symptoms to adjust ustekinumab dose vs standard of care (SoC) ustekinumab dose adjustment.[5] The primary endpoint was endoscopic response (50% or greater reduction in Simple Endoscopic Score for Crohn's Disease [SES-CD] vs baseline) at week 48. The inclusion criteria for the study were patients with active CD (Crohn's Disease Activity Index [CDAI] ≥220 and ≤450, and SES-CD ≥3), and patients who were either biologic-naive or previously exposed to only 1 biologic. At week 0, all participants received an intravenous induction treatment dose of approximately 6 mg/kg ustekinumab. At week 8, all participants received a 90 mg subcutaneous injection of ustekinumab. At week 16, participants who did not achieve a CDAI improvement of at least 70 points from baseline (CDAI 70) left the study. Remaining participants were randomized in a 1:1 ratio to the T2T

arm or SoC arm for open-label maintenance treatment up to week 48. At week 48, all remaining participants underwent colonoscopy.

The initial ustekinumab dosing interval in the T2T arm was based on week 16 endoscopy improvement from baseline SES-CD (<25% improvement assigned to ustekinumab every 8 weeks; ≥25% improvement assigned to ustekinumab every 12 weeks).[5] In the SoC arm, maintenance dosing intervals were in compliance with the Ustekinumab European Union Summary of Product Characteristics. Dose adjustments were based on disease flare as confirmed by the patient's physician. In the T2T arm, ustekinumab dosing intervals were based on the achievement of the target, defined as CDAI of less than 220 and at least 70-point improvement from baseline, and C-reactive protein (CRP) 10 mg/L or less or fecal calprotectin 250 μg/g or less. At follow-up visits in the T2T arm, if the target was not reached, the ustekinumab dose was escalated (ustekinumab every 12 weeks escalated to every 8 weeks, ustekinumab every 8 weeks escalated to every 4 weeks, and patients on ustekinumab every 4 weeks without reaching the target withdrew from the study).

There was a greater proportion of patients who achieved the primary endpoint of endoscopic improvement (SES-CD improvement ≥50% at week 48 compared with baseline) in the T2T arm than in the SoC arm (37.7% vs 29.9%, respectively; *P*=.093) when analyzed by nonresponder imputation (NRI).[5] The difference was nominally statistically significant if analyzed as last observation carried forward (40.0% vs 30.8%; *P*=.049) and as NRI including discontinuation only related to inefficacy (43% vs 32.3%; *P*=.036) (Figure).

Secondary outcomes included comparisons of clinical outcomes and biomarkers at week 48.[5] When analyzed as NRI, CDAI 70 (77.8% vs 69.5%; *P*<.05), clinical response (77.9% vs 68.2%; *P*<.05), and clinical remission (69.7% vs 61.4%; *P*=nonsignificant) were all numerically higher in the SoC arm compared with the T2T arm, with both CDAI 70 and clinical response statistically significant. When analyzed as last observation carried forward, no significant differences between the T2T and SoC arms were observed. Further, no significant differences between treatment arms were observed in changes in fecal calprotectin or CRP from baseline to week 48.

Discussion

The STARDUST trial provides further data to understand the implications of T2T approaches. Both the T2T and SoC arms showed high rates of endoscopic improvement, clinical response, and remission at 48 weeks with ustekinumab, and based on NRI, no benefit was observed in the T2T arm compared with the SoC arm. Clinical guidelines from the American College of Gastroenterology in 2019 and expert consensus statements (such as STRIDE-II, Selecting Therapeutic Targets in Inflammatory Bowel Disease, by the International Organization for the Study of Inflammatory Bowel Disease in 2021) recommend symptomatic and endoscopic remission as preferred treatment targets in patients with IBD and suggest changing treatment iteratively in order to achieve an endoscopic remission target.[6-8] In a randomized explanatory trial (CALM) of T2T in adalimumab-treated patients with CD, Colombel and colleagues found that treatment optimization using clinical biomarkers was more effective than treatment adjustment based on symptoms alone in achieving corticosteroid-free symptomatic remission as well as endoscopic remission at 1 year.[9] Unlike the STARDUST trial, the initial dose adjustment in CALM was not based on endoscopic activity, and CALM studied dose escalation of adalimumab rather than ustekinumab. In a related study evaluating early combined immunosuppression vs SoC, REACT used a cluster-randomized design to study early combined immunosuppression.[10] Practices were randomized to an early combined immunosuppression approach consisting of serial reassessment every 12 weeks and subsequent dose escalation of adalimumab or addition of an antimetabolite using a predefined algorithm until clinical remission was achieved. No statistically significant difference in the primary outcome of corticosteroid-free remission at 12 months was observed; however, secondary outcomes of complications were lower in the early combined immunosuppression arm at 24 months compared with conventional management. In addition, 2 single-center retrospective studies, one focused on ulcerative colitis and another on CD, showed that iterative changes in treatment based on endoscopic findings were strongly associated with mucosal healing.[11,12] Another retrospective study on CD found independent associations of mucosal healing with time between endoscopic procedures and adjustment of medical therapy when mucosal healing was not achieved.[13]

How does the STARDUST trial expand understanding of T2T for CD? Regarding the primary outcome, there was a numerical but not statistically significant difference in SES-CD improvement in T2T at week 48. One explanation is that T2T may require longer follow-up to observe benefit. REACT also showed no significant difference at 12 months, but a reduction in complications was seen at 24-month follow-up. Continued evaluation of longer-term outcomes from the STARDUST trial will be informative.

Despite being a negative study, the STARDUST trial resulted in several observations in subgroup analyses

that may identify patients for whom T2T is potentially beneficial. There were several subgroups that experienced a benefit of T2T over SoC for endoscopic response at 48 weeks: patients with longer disease duration (median of >79.1 months; odds ratio [OR], 2.15 [1.17-3.94]), less activity at baseline (CDAI ≤300; OR, 1.71 [1.04-2.80]), lower fecal calprotectin at baseline (≤250; OR, 3.03 [1.22-7.56]), endoscopically active disease at baseline (OR, 1.80 [1.11-2.94]), history of a disease-modifying event (eg, stricture, fistula, abscess, hospitalization, surgery; OR, 2.31 [1.06-5.01]), or a disease-modifying event at baseline (OR, 3.46 [1.07-11.19]). Although subgroup analyses must be interpreted with caution, they may inform how future studies of T2T may be optimized. It is relevant that no subgroup significantly favored SoC over T2T. Most subgroups that favored T2T over SoC were those with more advanced disease (ie, longer disease duration, endoscopic activity at baseline, and a history of complication or an ongoing complication at baseline). However, subgroups of patients with lower CDAI and lower fecal calprotectin were also more likely to benefit from T2T than SoC. Subgroups that demonstrated benefit from T2T are difficult to reconcile, as patients with lower CDAI and fecal calprotectin would be expected also to have less endoscopic activity and fewer disease-modifying events. Higher endoscopic activity at baseline may have been expected to be more likely to result in endoscopic response, as endoscopic activity at week 16 was used to stratify patients to higher dose ustekinumab maintenance. The reason patients with lower CDAI and fecal calprotectin at baseline were more likely to achieve endoscopic response with T2T is unclear and deserves further study.

Another interesting finding in the STARDUST trial was that there were numerical and statistically higher rates of CDAI 70 and clinical response at 48 weeks in the SoC arm vs the T2T arm using NRI analyses. Although this may seem contrary to the hypothesis of improved outcomes with T2T, this observation may highlight an important consideration of T2T approaches. It is worthwhile to note that the clinical outcomes were nearly identical on last observation carried forward analyses. Patients in the T2T arm were algorithmically escalated to ustekinumab every 4 weeks, and patients who did not achieve the target while on ustekinumab every 4 weeks discontinued the study. This means that patients potentially in clinical remission discontinued the T2T arm (if CRP >10 mg/L or fecal calprotectin >250 μg/g) and counted as failures on NRI analyses. Although not specified in the data presented to date, the observation of 19.9% discontinuation in the T2T arm vs 12.8% in the SoC arm and the nearly identical numbers in last observation carried forward analyses suggest this may be a contributing factor to the difference observed in the NRI analyses. This observation highlights the relevant concern for T2T approaches: what should be done for patients who never reach the target? T2T algorithms recommend continued escalation if normalization of biomarkers is not achieved. However, in the STARDUST trial, complete biomarker response (normalization of both CRP and fecal calprotectin) was achieved in only 30% of patients. Considering that 89.6% of T2T patients were in clinical response and 78.3% in clinical remission in the STARDUST trial, how much further escalation should be performed in patients who are in clinical remission?[5] Perhaps needed is a new classification for patients in clinical response/remission with residual inflammation rather than considering them treatment failures. Patient preference and shared decision-making in switching therapy while in clinical response/remission is another important factor and has not been considered in any of the prospective trials. Furthermore, there may be substantial patient burden in dealing with insurance approval and potentially higher copayments that need to be considered with T2T-based dose escalation or medication change.

Another consideration regarding interpretation of STARDUST trial findings is related to ustekinumab dosing intervals. Most patients were initiated on ustekinumab every-12-week dosing, which is not the labeled maintenance dose in the United States, although by week 48, most patients in the SoC arm were escalated to every-8-week dosing. Although CALM observed a benefit at escalation of adalimumab and an antimetabolite in 1-year outcomes, generalization of dose escalation in ustekinumab may not be appropriate, and differences in outcomes may take longer to observe. Lastly, STARDUST, CALM, and REACT did not incorporate therapeutic drug monitoring in decisions regarding dose escalation vs medication change, which may have diluted the effect of escalation by including patients for whom dose escalation would not be indicated.

Summary

The STARDUST trial provides additional data to understand the role of T2T in CD treatment. Although no significant difference was observed by NRI analysis for the primary outcome of endoscopic improvement in T2T vs SoC, high levels of clinical response, remission, and biomarker response at 48 weeks of ustekinumab were observed in both arms. Longer-term follow-up may be needed to observe the benefit of T2T. Additional study is needed to understand how to manage patients in clinical response or remission with persistent evidence of inflammation and how to consider patient shared

decision-making and patient burden related to T2T-based dose escalation or medication change.

Disclosures

Dr Gurwara has no relevant conflicts of interest to disclose. Dr Hou has received research funding from RedHill Biosciences, Janssen, AbbVie, Celgene, Genentech, Eli Lilly, Lycera, American Regent, and Pfizer.

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