

IM-UNITI at three years: stellar Stelara or stardust?

The efficacy, safety, and immunogenicity of ustekinumab treatment of Crohn's disease

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The three year results of ustekinumab for the treatment of Crohn's disease are published in this issue of the Journal [1]. Should we be impressed? Is this stellar Stelara, stardust, or a twinkle in the sky of Crohn's disease? Key questions arise: what are the headline results; how do they compare with anti-TNF or anti-integrin therapy; what about safety and immunogenicity and will more-specific anti-IL23 therapy offer patients (and their physicians) real advantage? But first, a brief synopsis of terminology for those who are neither anoraks nor have their telescopes fixed on the stars. IM-UNITI was the 44 week maintenance arm of the two induction studies, UNITI-1 (for patients exposed to anti-TNF therapy) and UNITI-2 (for patients naïve to anti-TNF therapy) [2]. ADHERE was the long term extension of CHARM, the adalimumab induction and maintenance trial for Crohn's disease [3,4]. GEMINI LTS (note the analogy with heavenly twins) was the long term follow up of vedolizumab induction and maintenance, with some patients directly enrolled [5].

How do the results compare with long-term anti-TNF or anti-integrin therapy?

Recognising the challenges of cross-study comparisons (Table), due to differences in study populations, extracting comparable data, efficacy measures, statistical analysis and study designs, it is difficult to compare these results with previous adalimumab or vedolizumab long-term extension data. Add to this the complexity of design: in IM-UNITI LTE, patients were enrolled from 6 groups, making it difficult to track progress, or even to answer simple questions about the proportion of patients previously exposed to anti-TNF therapy. However, the maintenance of efficacy with ustekinumab in patients with Crohn's disease was stable over 152 weeks of treatment, even though 60% had previously been exposed to anti-TNF therapy [1]. Nevertheless, in GEMINI LTS, with comparable anti-TNF exposure (65%), almost 90% of initial responders to vedolizumab sustained remission at 152 weeks [5]. This is notable, because patients appeared to have a higher degree of activity at trial entry, with just 33% in 'remission' for GEMINI LTS and 69% for IM-UNITI – although one of the many limitations of the Table is that indices differ. The 'non-responder' imputation rate on vedolizumab was much lower (43%), because many patients had yet to complete 152w of therapy and were included with the drop outs as 'non-responders'. An impression is evolving that the effect of anti-integrin therapy is more sustainable than anti-TNF therapy, so the sustainability of anti-IL23 therapy is of clinical relevance. As presented in this analysis of IM-UNITI, it has some way to go and it matters, because the initial choice of therapy is influenced not only by initial efficacy (apparently stuck at around 30% for all agents), but also by the likelihood of having to change targets if remission is not achieved. The relatively high steroid-free remission rate (56%) in IM-UNITI is encouraging, although the high proportion of patients with Crohn's who continue to receive steroids in many clinical trials always seems remarkable. It appears that treatment with steroids is a default position for some physicians, despite international guidelines to the contrary [7].

What about safety and immunogenicity?

Safety matters and for some patients, safety matters most. The results of IM-UNITI are very encouraging. Furthermore, the low immunogenicity (<5%) suggests that combotherapy with immunomodulators such as thiopurines or methotrexate is unnecessary. This will appeal to patients and their physicians. Rates of immunogenicity are, however, notoriously difficult to compare, owing to different assays and masking of antibody detection by circulating drug. Since the long term safety of thiopurines is increasingly questioned [8] and anti-TNF therapy is associated with a doubling of the risk of opportunistic infection [9], it helps to have access to therapy with no more serious adverse events than placebo. Patients will still need to understand the risks of under-treating moderate to severely active Crohn's disease, for whom 'no treatment' is rarely an option in the real world.

Does everyone need ustekinumab e8w?

The answer to this depends on whether you see your glass half full, or half empty. On the one hand the difference in clinical remission rates at 152w on ustekinumab 90mg every 8w (e8w) compared to

every 12w (e12w) is marginal. Among patients entering the long-term extension in their original randomized groups, 70% of e8w patients were in remission at Week 152, compared to 62% on e12w. However, across all ustekinumab-treated patients entering the long-term extension, remission rates at 152w were 55% and 56% for e8w and e12w, respectively, even though the time to loss of response was longer with more frequent dosing ($p=0.044$). Yet it probably matters for patients who have received anti-TNF therapy in the past: numbers are small, but 16/27 (59%) patients on e8w were in remission at 152w from UNITI-1, compared to 14/32 (44%) on e12w; this compares to 75% and 73% respectively from UNITI-2 (no prior exposure). It remains to be seen whether the 'one-size fits all' dose of 90mg is indeed appropriate for all patients regardless of weight and disease activity.

Will more specific anti-IL23 offer real advantage?

There are many questions that remain while anti-IL23 finds its place in the therapeutic armamentarium for Crohn's disease. Included are questions about mucosal healing and efficacy in treating fistulae; another is whether it can alter disease progression, although the long duration of pre-existing disease in all registration trials of advanced therapy (8-10y) means that we cannot reasonably expect this to be answered, however long the follow up. On the other hand, the safety and low level of immunogenicity demonstrated by IM-UNITI should be a stimulus to early treatment trials. A further question is whether therapy targeted at the p19 subunit of the IL-23 receptor (eg mirikizumab or risinkizumab, among others) will have an advantage over ustekinumab. Initial results from the UltIMMa trials in psoriasis, with a head to head comparison of ustekinumab and risinkizumab, suggests that it may. The 90% skin healing rate (PASI 90) score was 42% on ustekinumab and 75% on risinkizumab ($p<0.0001$) [10]. Crohn's disease is not psoriasis of the gut, but this is promising and we live in exciting times.

IM-UNITI establishes anti-IL23 therapy as effective therapy in the longer term management of moderate to severely active Crohn's disease, whether or not patients have received anti-TNF therapy in the past. For patients who are naïve to anti-TNF therapy, then a dose of ustekinumab 90mg e12w is as effective as e8w. For patients previously exposed to anti-TNF therapy, then ustekinumab 90mg e8w may carry an advantage.

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Table

Item	Ustekinumab	Adalimumab	Vedolizumab
Acronym	IM-UNITI LTE ¹ [1,2]	ADHERE [3,4]	GEMINI-LTS [5,6]
Number enrolled	567	467	1297
Population/entry criteria	Completed w44 of IM-MUNITI, or w52 after induction	Completed w56 of CHARM	Completed w52 of GEMINI 2 or withdrew early and continued VDZ, completed w10 of GEMINI 3, or direct enrolment
Follow up duration (average, weeks from induction baseline)	142	212	88 ⁶
Dropouts n/enrolled (%)	168/567 (30)	188/467 (40)	495/1297 (38)
Anti-TNF naïve at initial trial entry n (%)	157/397 (40)	390/778 (50)	447/1295 (35)
Dose flexibility during long term extension	No	Yes	No
Disease duration (average of means across groups, yr)	10.1	8.1	10.2
Age (average of means across groups ²)	38.7	37.2	37.7
Location Ileal (L1, %)	16	-	16
Colonic (L2, %)	20	-	25
Ileocolic (L3, %)	64	-	59
Perianal (p, %)	32	9	46
Disease activity at entry ³ (median score)	110 (CDAI)	175 (CDAI)	8 (HBI)
(CRP, mg/L)	3.8	-	14.9
(remission, %)	69	43	33
Primary endpoint	Remission ³ at w152	Remission at w212	Safety; remission pre-specified 2 ^o
Clinical remission at endpoint (in all responders, including dose adjustment)	60% (LOCF)	30% (NRI) 57% (LOCF)	43% ⁷ (NRI) 89% (as observed)
Clinical remission (responders at w52-56, intention to treat)	62% q12w 70% q8w	54% (NRI) 80% (LOCF)	NA
Corticosteroid-free remission ⁴	52% (LOCF)	16% (ITT)	-
Mucosal healing at endpoint	-	-	-
Number of SAE (per 100 patient years)	19.0 (UST ⁵) 19.5 (PBO)	31.0	25.1 (VDZ) 31.8 (PBO)
Antibody formation	4.6%	-	2-4%

Table legend

¹IM-UNITI LTE: patients continued the same treatment they were receiving at Week 44 (subcutaneous [SC] placebo, ustekinumab 90mg every 8 weeks [q8w] or every 12 weeks [q12w]) with no dose adjustment in the long term extension [LTE]; ²Average of means across groups: calculated from published tables in the absence of access to the original data; ³Remission: Crohn's disease activity index <150 points, except for vedolizumab: Harvey Bradshaw Index ≤4; ⁴Corticosteroid free remission: CDAI <150 and no corticosteroids at w152; ⁵UST: all ustekinumab-treated patients; ⁶Max follow up duration: 616d (88w) from 57w (directly enrolled) to 219w (GEMINI 2), all treated with vedolizumab 300mg every 4 w. ⁷Only patients from GEMINI 2 entering LTS, at

w152 (n=145 NRI, n=70 as observed); ⁷VDZ: all vedolizumab-treated patients in trials of Crohn's disease

PBO: placebo; LOCF: last observation carried forward; NRI: non-responder imputation; ITT: intention to treat from induction baseline; NA: not applicable All percentages are rounded to the nearest integer, unless <10%. Results between trials are not strictly comparable, owing to differences in study populations, extractable data, efficacy measures, statistical analysis and study designs