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Primary imputation methods impact efficacy results in hidradenitis suppurativa clinical trials

To the Editor: Missing data is a common issue in clinical trials. Analytic management of missing data involves including participants who drop out of a study in an intention-to-treat (ITT) analysis.[1] Analyzing only participants who complete a trial (per protocol [PP]) can eliminate missing data but at the expense of statistical power and external validity.[1] If the participant and disease-associated characteristics of those who completed the trial are representative of the ITT population, then PP can be valid. This is particularly important in placebo-controlled trials, where using PP may decrease the ability to detect a difference between groups (because only participants receiving placebo with a positive response tend to stay in the trial).[1]

In ITT, management of missing data involves primary imputation of missing values (Table I).[1] Multiple imputation involves complex statistical modeling and is beyond the scope of this discussion; the reader is directed to the statistical literature (Supplemental Materials; available via Mendeley at https://doi.org/10.17632/h8734gr7bc.1).[1] Primary imputation involves allocating participants a response based on the reasons/assumptions for missing data. Data can be classified as *missing not at random* (due to treatment-related factors, eg, lack of efficacy), *missing at random* (due to other documented factors such as age/sex that can be taken into account in multiple imputation), or *missing completely at random* (due to other undocumented variables not related to disease/treatment).[1] A sensitivity analysis (comparison of multiple primary imputation methods) is required to determine the effect of different analyses on the outcome(s) of interest.[1] This is especially pertinent given that clinical trial populations are not directly reflective of the general population.[1]

In the setting of hidradenitis suppurativa (HS), the high burden of disease and moderate therapeutic response rates may contribute to the high clinical trial dropout rates. The statistical methods used in these trials (Table II) vary, making comparisons complex. The PIONEER 1 and 2 studies were the only studies to conduct a sensitivity analysis,[2] conservatively presenting results of nonresponder imputation analysis. In contrast, the PIONEER Open Label Extension study[3] presented only PP data from a subset of participants, with last observation carried forward (LOCF) beyond week 96. This raises concerns regarding data validity, given that LOCF inflates response rates in long-term studies and is not recommended.[1] The use of ITT/nonresponder imputation in a randomized controlled trial of anakinra[4] in HS resulted in a loss of statistical significance. No dropout was seen in a phase 2a trial of IFX-1,[5] with differential attrition seen between arms of a phase 2 trial of bermekimab.[6] This may explain the apparent contradictory findings of an increased response rate in participants for whom anti−tumor necrosis factor (TNF) therapy failed (63%) when compared with anti-TNF−naive participants[6] (61%). Given that all participants who dropped out in the anti-TNF−failed arm achieved hidradenitis suppurativa clinical response, this may erroneously conflate the true efficacy of the drug in this population. In a cohort study of secukinumab,[7] 71% of the participants who dropped out did not achieve HiSCR, suggesting that LOCF presents a more conservative estimate of response compared with PP analysis, although the characteristics of the participants who

Table I. Definitions of primary imputation terms

Primary imputation term	Description
Missing equals success (MES)	Individuals with missing data are presumed to have achieved the endpoint of interest
Missing equals failure (MEF)	Individuals with missing data are presumed to have not achieved the endpoint of interest (equivalent to NRI)
Nonresponder imputation (NRI)	Individuals with missing data are presumed to have not achieved the endpoint of interest (equivalent to MEF)
Last observation carried forward (LOCF)	Individuals with missing data are presumed to have maintained the last observation, extrapolated forward to all future timepoints including endpoints of interest

Table II. Sensitivity analysis of missing data analysis in hidradenitis suppurativa clinical trials

Clinical trial	Reported primary outcome (method)	PP analysis, n/N (%)	ITT analysis, n/N (%)			Participants who dropped out, n
			MES	MEF (NRI)*	LOCF	
PIONEER 1 (adalimumab vs placebo)	Week 12 HiSCR INT: 41.8% (ITT/NRI)	64/145 (44.1)	72/153 (47.1)	64/153 (41.8)	—	8 outcome (s) unknown
	Week 12 HiSCR PBO: 26% (ITT/NRI)	40/145 (27.6)	49/154 (31.8)	40/154 (26)		9 outcome(s) unknown
		CMH: $P < .01$	CMH: $P < .01$	CMH: $P < .01$		
PIONEER 2 (adalimumab vs placebo)	Week 12 HiSCR INT: 58.9% (ITT/NRI)	96/155 (61.9)	104/163 (63.8)	96/163 (58.9)	—	8 outcome(s) unknown
	Week 12 HiSCR PBO: 27.6% (ITT/NRI)	45/151 (29.8)	57/163 (35.0)	45/163 (27.6)		12 outcome(s) unknown
		CMH: $P < .001$	CMH: $P < .001$	CMH: $P < .001$		
PIONEER OLE (adalimumab)	Week 12 HiSCR INT: (PP)†	46/88 (52.3)	—	—	Used for data >week 96	Unable to calculate
Anakinra (vs placebo)	Week 12 HiSCR INT: 7/9 (78%) vs PBO: 3/10 (30%) (PP)	INT: 7/9 (78)	INT: 8/10 (80)	INT: 7/10 (70)	INT: 7/10 (70)	1 outcome unknown
		PBO: 3/10 (20) χ^2: $P = .04$	PBO: 3/10 (30) χ^2: $P = .02$	PBO: 3/10 (30) χ^2: $P = .07$	PBO: 3/10 (30) χ^2: $P = .07$	0
IFX-1 (C5a)	Day 50 HiSCR: 9/12 (75%)	9/12 (75)	9/12 (75)	9/12 (75)	9/12 (75)	No dropout
Bermekimab (IL-1a)	Week 12 HiSCR: TNF failed (63%) (ITT LOCF)	13/22 (59)	17/24 (71)	13/24 (54)	15/24 (63)	2/2 achieved HiSCR (100%)
	Week 12 HiSCR TNF naive (61%) (ITT LOCF)	7/11 (64)	13/18 (72)	7/18 (39)	11/18 (61)	4/7 achieved (57%)
Secukinumab (IL-17A)	Week 12 HiSCR: 13/20 (65%) (ITT LOCF)	11/13 (85)	11/13 (85)	11/20 (55)	13/20 (65)	2/7 achieved HiSCR (29%)

CMH, Cochran-Mantel-Haenszel method; *HiSCR*, hidradenitis suppurativa clinical response; *IL*, interleukin; *INT*, intervention; *ITT*, intention to treat; *LOCF*, last observation carried forward; *MEF*, missing equals failure; *MES*, missing equals success; *NRI*, nonresponder imputation; *OLE*, Open Label Extension; *PBO*, placebo; *PP*, per protocol.

*MEF and NRI in the context of these studies are interchangeable.

†LOCF was imputed for timepoints beyond 96 weeks, as per the methods.

dropped out requires comparison to the overall cohort to assess the relationship between dropout and disease-related factors.

The decision about the best method of analysis is based on the individual study and the characteristics of the participants who dropped out. Future HS clinical trials should report and discuss participant dropout, and readers should critically evaluate the methods used to understand and acknowledge the potential bias in results.

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Efficacy of oral zinc and nicotinamide as maintenance therapy for mild/moderate hidradenitis suppurativa: A controlled retrospective clinical study

To the Editor: Hidradenitis suppurativa (HS) is a chronic cutaneous disease that involves follicular occlusion in the apocrine gland-bearing regions. Treatment is a challenge because of the paucity of effective therapies and frequent exacerbations, with a negative impact on quality of life.[1] Brocard et al[2] first described zinc gluconate (90 mg daily for 4 months) as an effective therapeutic alternative for the management of HS. In our study, the efficacy of oral zinc and nicotinamide as maintenance treatment in mild to moderate HS was investigated retrospectively. A total of 92 patients affected by Hurley stage I and II HS were evaluated (Table I). All included patients had previously been treated with oral tetracycline (minocycline 100 mg daily) for 12 weeks with clinical and ultrasonographic benefit. The patients were divided into 2 groups according to treatment received or not received at the end of systemic antibiotic course. Specifically, 47 patients started oral therapy with capsules containing 90 mg of zinc gluconate and 30 mg of nicotinamide once daily for 90 days. The treated group was compared with a control group of 45 patients who did not receive any treatment. Each participant was evaluated at baseline and at 90 and 180 days after treatment. At 12 and 24 weeks, we observed a significant reduction in the number and mean duration of acute flares in the treated versus control groups. Patients of the treated group correspondingly reported a marked reduction in mean Visual Analogue Scale, Dermatology Life Quality Index, and International HS Severity Score System scores compared with the control group both at 12 and 24 weeks ($P < .005$). Disease-free survival was significantly longer in the treated group, and it showed sustained improvement even after discontinuation of oral supplementation. Slightly decreased or stable International HS Severity Score System score and pain Visual Analogue Score during the maintenance treatment was collaterally observed in the treated group with no statistically significant difference at 24 weeks (Table II). Two patients reported nausea; neither stopped the treatment. The use of oral zinc as a helpful treatment in HS (as monotherapy or in association with topical therapy) has been rarely described in the literature.[1-4] However, to our knowledge, no studies have investigated its usefulness as a maintenance treatment to potentiate the beneficial effects obtained with other agents, such as antibiotics, that are frequently used in HS. The efficacy of zinc could be related to its anti-inflammatory activity, inhibiting the chemotaxis of neutrophils, activating natural killer cells and the phagocytic function of granulocytes, and modulating the production of tumor necrosis factor α, interleukin 6, and metalloproteinases.[2,4] Additionally, it seems to have an antiandrogen activity, modulating 5α-reductase type I and II expression levels and activity.[2] Nicotinamide, as zinc, has anti-inflammatory and antioxidant activity by inducing the expression of the enzyme zinc/copper superoxide dismutase and reducing the accumulation of free radicals.[2,5] The main limitations of the study are the retrospective nature, with absence of a randomized, blinded control group. This study seems to suggest that zinc and nicotinamide supplementation in