RELATIONSHIP BETWEEN HOSPITALIZATION, SURGERY, AND ACHIEVEMENT OF CLINICAL REMISSION OR CLINICAL RESPONSE IN MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE PATIENTS: RESULTS FROM THE UNITI/IM-UNITI TRIALS

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BACKGROUND

Crohn's disease (CD) is a chronic, progressive inflammatory bowel disease (IBD) that is characterized by relapsing inflammation occurring in any part of the gastrointestinal tract, which may lead to symptoms like diarrhea, abdominal pain, cramping, fatigue, weight loss, fever, anemia, depression, and anxiety.[1-3]

Management and treatment of patients with CD is associated with substantial direct medical costs, out-of-pocket expenditures, and workplace productivity losses, resulting in a high burden for patients and payers.[4,5]

Three phase III UNITI/IM-UNITI trials (UNITI-1: NCT01369329; UNITI-2: NCT01369342; IM UNITI: NCT01369355) assessed the efficacy and safety of ustekinumab's induction and maintenance relative to placebo in patients with moderately to severely active CD; these trials also assessed hospitalization and surgery rates.

Understanding the relationship between rates of hospitalization and surgery and health states, including clinical remission, clinical response, and active CD, can help determine the economic burden.

OBJECTIVE

The objective of this analysis was to determine the relationship between hospitalization and surgery rates and health state over one year in patients with CD.

METHODS

- Data for hospitalization and surgery rates from UNITI/IM-UNITI were pooled across arms and across induction and maintenance phases.
  - The UNITI-1 and UNITI-2 trials assessed the efficacy and safety of ustekinumab induction therapy relative to placebo in patients with moderately to severely active CD; data from these trials were combined for induction.
  - The IM-UNITI trial assessed the efficacy and safety of ustekinumab maintenance therapy relative to placebo in patients with moderately to severely active CD.
- Based on clinical remission and response achieved at each visit (weeks 0-52), patient exposure times were classified into three health states using the Crohn's Disease Activity Index (CDAI) score:
  - Clinical remission was defined as a CDAI score of <150 points
  - Clinical response without clinical remission was defined as a reduction from week 0 of induction in the CDAI score of ≥100 points but CDAI score not <150 points
  - Active CD was defined as no response nor remission. All patients were categorized in active CD state at baseline.
- Hospitalization and surgery events were assigned based on the heath state at the visit prior to the event (**Figure 1**).
- The base case analysis was conducted on the safety population and evaluated CD-related hospitalizations and surgeries only.
- Two sensitivity analyses were conducted to test the robustness of the base case results:
  - Sensitivity Analysis 1: conducted on the safety population including both CD- and non CD-related hospitalizations and surgeries
  - Sensitivity Analysis 2: conducted on the efficacy population including patients who were in clinical response to ustekinumab induction therapy and were re-randomized to maintenance only
- Annualized hospitalization and surgery rates were estimated by health state adjusting for the exposure time in each health state.
- Proportions of patients hospitalized or who had surgery (per 100 patient-years of exposure time) in each health state were also estimated in order to provide patient-level results.
  - Patients with multiple hospitalizations or surgeries were accounted for and calculated as the number of patients with a hospitalization or who had surgery divided by the total number of hospitalizations or surgeries under a certain health state.
- A Poisson regression model was used to compare hospitalization and surgery outcomes across health states and generate P-values.

Figure 1. Categorization of hospitalization or surgery event in each health state

DISCUSSION AND CONCLUSIONS

- **Using hospitalization and surgery data from the UNITI/IM-UNITI trials, the results of the base case analyses showed that annualized hospitalization and surgery rates, as well as proportion of patients with CD-related hospitalizations or surgeries, were significantly lower among patients in clinical remission than among those in active CD.**
- **In the base case analysis, only the proportion of patients with a CD-related hospitalization was significantly lower among patients in clinical response without remission than among those in active CD, whereas differences for all other outcomes were numerically lower among patients in clinical response than among those in active CD.**
- **Furthermore, mean duration of CD-related hospitalization was numerically lower among hospitalized patients in clinical remission and clinical response without remission than among hospitalized patients in active CD.**
- **Results of the sensitivity analyses were generally consistent with those of the base case, highlighting the robustness of the analysis.**
- **The hospitalization rates in this analysis are largely consistent with those from a study by Lichtenstein and colleagues that used data from the National Inpatient Sample of the Healthcare Cost and Utilization Project in the US and reported a hospitalization rate of 22% over 54 weeks among patients with CD who spent 25%-50% of their time in remission.[6]**
- **Overall, the results of this study highlight that the healthcare resource utilization burden among patients with CD is substantially higher among patients in an active disease state than among those in remission, and to a lesser extent among patients who achieve a response without remission.**

RESULTS

Study population and demographics

- The total exposure in each health state was 430.5, 264.4, and 552.4 years for patients in clinical remission (n=773), clinical response (n=723), and active CD (n=1,255), respectively.
- 148 patients had hospitalization events and 90 patients had surgery (**Table 1**). Significant differences were observed between the full study population, hospitalized patients, and patients who had surgery, including age, race, and region.

Table 1. Baseline demographics of patients with CD from the UNITI/IM-UNITI Trials

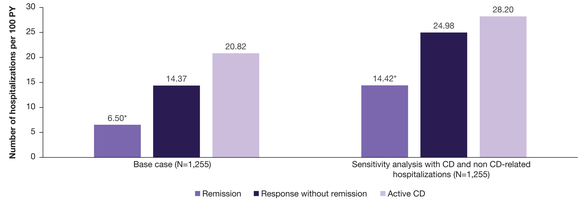
	Full study population N=1,255	Hospitalized Patients N=148	Patients who had surgery N=90	Full study population vs. hospitalized patients *P*-value	Full study population vs. patients who had surgery *P*-value
Sex, n (%)					
Female	696 (55.5%)	85 (57.4%)	52 (57.8%)	0.65	0.67
Male	559 (44.5%)	63 (42.6%)	38 (42.2%)		
Age in years, mean (SD)	38.2 (12.6)	36.0 (12.1)	35.8 (10.8)	**0.04**	0.07
Race, n (%)					
White	1,059 (84.4%)	116 (78.4%)	64 (71.1%)		
Asian	100 (8.0%)	16 (10.8%)	14 (15.6%)		
Black or African American	39 (3.1%)	9 (6.1%)	5 (5.6%)	0.32	**0.03**
Other	36 (2.9%)	5 (3.4%)	3 (3.3%)		
Not reported	17 (1.4%)	2 (1.4%)	3 (3.3%)		
Unknown	4 (0.3%)	0 (0%)	1 (1.1%)		
Region, n (%)					
Asia	96 (7.7%)	16 (10.8%)	14 (15.6%)		
Eastern Europe	166 (13.2%)	8 (5.4%)	3 (3.3%)	**0.01**	**<0.01**
Rest of the world	993 (79.1%)	124 (83.8%)	73 (81.1%)		

Note: Total percentages may not sum to 100% due to rounding.
Abbreviations: CD = Crohn's disease; SD = standard deviation.

Hospitalizations

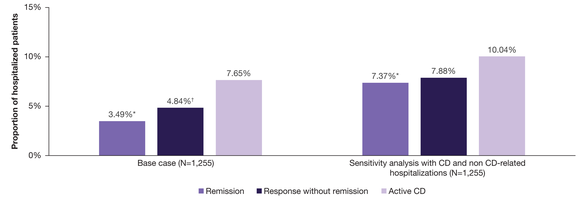
- Base case analysis for CD-related hospitalizations:
  - The annualized hospitalization rates were significantly lower among patients in clinical remission (0.0650) and numerically lower among patients in clinical response without remission (0.1437) than in patients in active CD (0.2082; $P < 0.0001$ and $P = 0.10$, respectively).
    - These results can be interpreted as 6.50 hospitalizations per 100 patient-years (PY) in clinical remission, 14.37 hospitalizations per 100 PY in clinical response without remission, and 20.82 hospitalizations per 100 PY in active CD (**Figure 2**).
  - The proportions of patients hospitalized were significantly lower among those in clinical remission and clinical response without remission than in those in active CD (3.49% and 4.84% vs. 7.65%, $P < 0.01$ and $P = 0.02$, respectively) (**Figure 3**).
- Sensitivity analyses for CD-related hospitalizations:
  - Sensitivity Analysis 1:
    - Annualized hospitalization rates and the proportions of hospitalized patients were significantly lower among patients in remission ($P < 0.0001$ and $P < 0.01$, respectively) and numerically lower among patients in response without remission than among those in active disease (**Figure 2** and **Figure 3**).
  - Sensitivity Analysis 2:
    - Annualized hospitalization rates were significantly lower among patients in remission and among patients in response without remission than among those in active disease (7.28 and 11.54 vs. 29.13 hospitalizations per 100 PY, $P = 0.004$ and $P = 0.04$, respectively).
    - The proportions of hospitalized patients were numerically, but not significantly, lower among patients in remission and among patients in response without remission than among those in active disease (4.22% and 4.07% vs. 5.41%, $P = 0.46$ and $P = 0.43$, respectively).

Figure 2. Annualized hospitalization rates in UNITI/IM-UNITI trials in each health state for the base case analysis and Sensitivity Analysis[1]



**P < 0.05 between clinical remission and active CD.*
Abbreviations: CD = Crohn's disease; PY = patient year.

Figure 3. Proportion of patients with CD-related hospitalization in each health state for the base case analysis and Sensitivity Analysis[1]

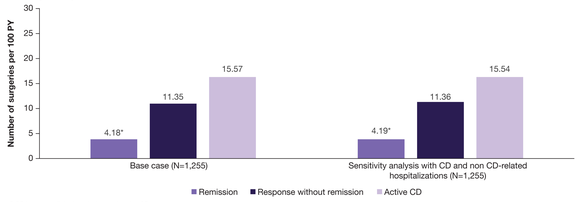


**P < 0.05 between clinical remission and active CD. †P < 0.05 between clinical response without remissions and active CD.*
Abbreviations: CD = Crohn's disease.

Surgeries

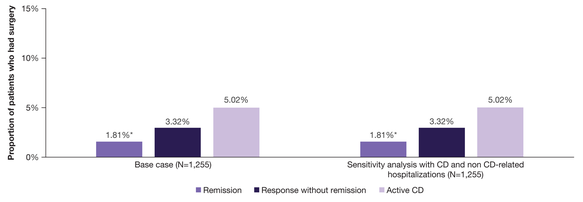
- Base case analysis for CD-related surgeries:
  - Patients in clinical remission had a significantly lower annualized surgery rate than those in active CD (0.0418 vs. 0.1557, $P < 0.0001$); no significant difference in annualized surgery rate was observed between patients in clinical response without remission and those in active CD (0.1135 vs. 0.1557; $P = 0.30$).
    - These results can be interpreted as 4.18 surgeries per 100 PY in clinical remission, 11.35 surgeries per 100 PY in clinical response without remission, and 15.57 surgeries per 100 PY in active CD (**Figure 4**).
  - Similarly, the proportion of patients who had surgery was significantly lower among those in clinical remission (1.81%) and numerically lower among those in clinical response without remission (3.32%) than in those in active CD (5.02%; $P < 0.01$ and $P = 0.08$, respectively) (**Figure 5**).
- Sensitivity analyses for CD-related surgeries:
  - Sensitivity Analysis 1:
    - Annualized surgery rates and the proportions of patients who had surgery were significantly lower among patients in remission ($P < 0.0001$ and $P < 0.01$, respectively) and numerically lower among patients in response without remission than among those in active CD.
  - Sensitivity Analysis 2:
    - Annualized surgery rates were significantly lower among patients in remission and numerically lower among patients in response without remission than among those in active CD (3.40 and 11.54 vs. 14.56 surgeries per 100 PY, $P = 0.03$ and $P = 0.44$, respectively).
    - The proportions of patients who had surgery were low and similar between patients in remission and patients in response without remission compared with patients in active CD (1.81% and 2.59% vs. 1.80%, $P = 0.99$ and $P = 0.49$, respectively).
      - In this smaller subset of patients who responded to ustekinumab, rates of surgery were markedly lower among patients in response without remission and those in active disease compared with the other analyses.
      - Several factors may have contributed to this finding, including fewer non-remission disease state events in this subset, a carry-over effect of the initial ustekinumab response, the re-initiation of rescue corticosteroids, and crossover to active treatment for those patients losing response.

Figure 4. Annualized surgery rates in UNITI/IM-UNITI trials in each health state for the base case analysis and Sensitivity Analysis[1]



**P < 0.05 between clinical remission and active CD.*
Abbreviations: CD = Crohn's disease; PY = patient year.

Figure 5. Proportion of patients with CD-related surgeries in each health state for the base case analysis and Sensitivity Analysis

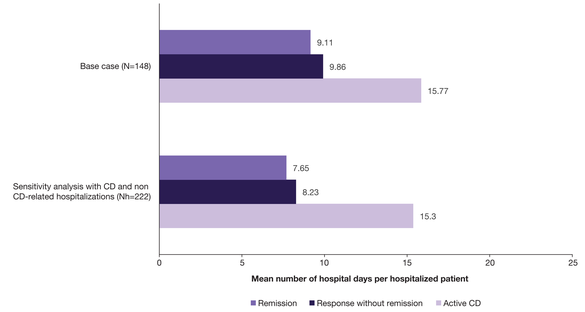


**P < 0.05 between clinical remission and active CD.*
Abbreviations: CD = Crohn's disease; PY = patient year.

Hospitalization Duration

- Patients in clinical remission (9.11 days) and clinical response (9.86 days) also had a numerically shorter mean duration of hospitalization compared to patients in active CD (15.77 days) (**Figure 6**).
  - Results of the sensitivity analyses for mean duration of hospitalization were generally consistent with those of the base case analysis.
    - Sensitivity Analysis 1: patients in clinical remission and clinical response had a numerically shorter mean duration of hospitalization than patients in active CD (**Figure 6**).
    - Sensitivity Analysis 2: patients in clinical remission (9.86 days) and clinical response (7.00 days) had a numerically shorter mean duration of hospitalization than patients in active CD (20.81 days).

Figure 6. Mean number of hospital days per hospitalized patient for the base case analysis and Sensitivity Analysis[1]



Abbreviations: CD = Crohn's disease; Nh = number of hospitalized patients in each analysis.

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Disclosure

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