Inflammatory Bowel Disease Best of DDW 2022

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Withdrawal of Infliximab or Anti-metabolite Therapy in CD Patients in Sustained Remission on Combination Therapy **SPARE Trial**

- Background:
  - Combination therapy with infliximab and anti-metabolites is a standard therapeutic option for patients with CD
  - Implications of long-term combination therapy may lead patients and clinicians to contemplate treatment de-escalation once steroid-free remission has been achieved

- Aim:
  - To assess the relapse rates and time spent in remission over 2 years after withdrawal of infliximab or anti-metabolite compared continuation of combination therapy

Laharie et al. Presented at DDW. 2022.

Withdrawal of Infliximab or Anti-metabolite Therapy in CD Patients in Sustained Remission on Combination Therapy **SPARE Trial**

- Methods:
  - International, multicenter, randomized, unblinded controlled trial
  - CD patients treated with combination therapy of infliximab and anti-metabolite > 8 months and in sustained steroid-free remission > 6 months
  - Patients were randomized to one of three arms:
    - Arm A: continuing combination therapy
    - Arm B: stopping infliximab
    - Arm C: stopping anti-metabolite
  - In case of relapse, patients were retreated by resuming infliximab (Arm B) or the anti-metabolite (Arm C)

Laharie et al. Presented at DDW. 2022.

Withdrawal of Infliximab or Anti-metabolite Therapy in CD Patients in Sustained Remission on Combination Therapy **SPARE Trial**

- Primary endpoints:
  - Relapse rate and mean survival team spent in remission over 2 years
- Secondary endpoints:
  - Treatment failure defined as complications or not recapturing remission

Laharie et al. Presented at DDW. 2022.

Withdrawal of Infliximab or Anti-metabolite Therapy in CD Patients in Sustained Remission on Combination Therapy **SPARE Trial**

- Results:
  - 205 patients analyzed: 67 in Arm A (combination therapy), 71 in Arm B (infliximab discontinuation), 67 in Arm C (anti-metabolite discontinuation)

Parameters	arm A (n=67)	arm B (n=71)	Arm C (n=67)
Age (yrs) (med, IQR)	36 (27-45.5)	32 (25-42.5)	31 (26-44)
Female Gender (n, %)	30 (44.8)	28 (39.4)	31 (46.3)
Disease dur. (yrs) (med, IQR)	6.4 (3.2-12.7)	6.7 (3.3-10.7)	6.8 (2.8-12.7)
CRP (mg/l) (med, IQR)	1.3 (0.5-2.9)	1.3 (0.6-2.8)	1.2 (0.5-2.6)
Fecal Cal (µg/g) (med, IQR)	95 (23-425)	95 (28-305)	85 (24-201)
Ulcers at endosc (n, %)	8 (11.9)	8 (11.3)	5 (7.5)
CDEIS (med, IQR)	0 (0-0)	0 (0-0)	0 (0-0)

Laharie et al. Presented at DDW. 2022.

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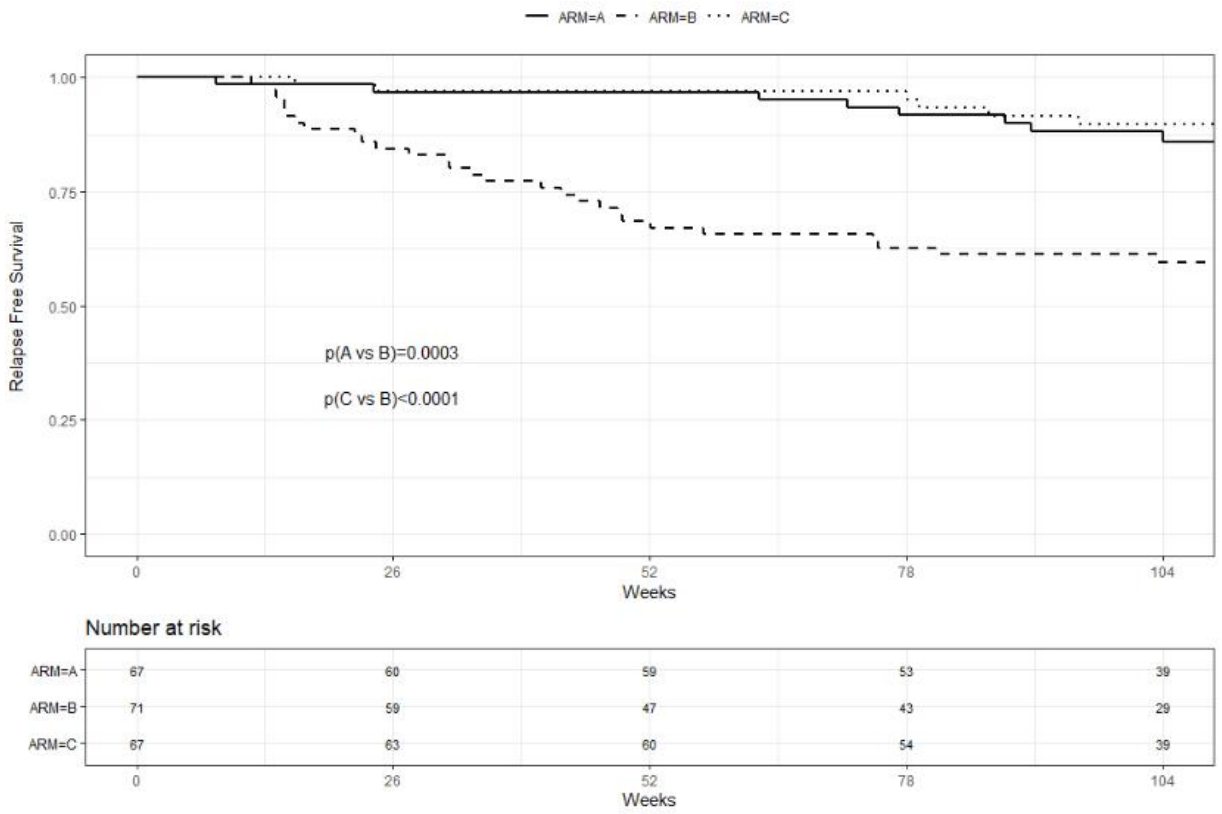
Arms	2 Year Relapse Rates	Time Spent in Remission (years)
A - Combination Therapy	14% (95% CI 4-23)	1.91 (95% CI 1.83-1.99)
B - Infliximab Discontinuation	40% (95% CI 28-51)	1.89 (95% CI 1.82-1.96)
C - Anti-metabolite discontinuation	10% (95% CI 2-18)	1.93 (95% CI 1.86-2.00)

Laharie et al. Presented at DDW. 2022.

Withdrawal of Infliximab or Anti-metabolite Therapy in CD Patients in Sustained Remission on Combination Therapy **SPARE Trial**



Laharie et al. Presented at DDW. 2022.

Withdrawal of Infliximab or Anti-metabolite Therapy in CD Patients in Sustained Remission on Combination Therapy **SPARE Trial**

- 39 patients relapsed, meaningful predictors of relapse:
  - Infliximab withdrawal
  - Young age at diagnosis (<17 years)
  - Fecal calprotectin >300 mcg/g at withdrawal

- 28 were retreated/optimized, remission was achieved in:
  - Arm A: 1/2
  - Arm B: 22/23
  - Arm C: 2/3

Laharie et al. Presented at DDW. 2022.

Withdrawal of Infliximab or Anti-metabolite Therapy in CD Patients in Sustained Remission on Combination Therapy **SPARE Trial**

- Conclusions:
  - Infliximab withdrawal, but not anti-metabolite withdrawal, was associated with a significantly higher risk of relapse than continuation of combination therapy
  - Almost all patients who discontinued infliximab achieved rapid remission when treatment was resumed
  - The mean time spent in remission over 2 years was similar across groups

Laharie et al. Presented at DDW. 2022.

Vedolizumab Intravenous is Effective Across Multiple Treatment Targets in Chronic Pouchitis
EARNEST Trial

- Background:
  - Acute pouchitis occurs in 50-80% of patients after TPC with IPAA, and up to 20% of patients will progress to chronic pouchitis
  - There are currently no approved therapies for chronic pouchitis

- Aim:
  - To assess the efficacy and safety of vedolizumab in patients with chronic pouchitis defined as modified Pouchitis Disease Activity Index (mPDAI) score > 5 and a minimum endoscopic sub-score of 2 with either:
    - > 3 recurrent episodes of pouchitis within 1 year treated with > 2 weeks of antibiotics
    - Maintenance antibiotic therapy > 4 weeks

Lightner et al. Inflamm Bowel Dis. 2017.
Travis et al. Presented at DDW. 2022.

Vedolizumab Intravenous is Effective Across Multiple Treatment Targets in Chronic Pouchitis
EARNEST Trial

- Methods:
  - Randomized, double-blind, placebo-controlled study
  - Patients 18-80 years old with chronic pouchitis randomized to ciprofloxacin for the first 4 weeks and either vedolizumab (300 mg) or placebo on day 1 and weeks 2, 6, 14, 22, and 30

Travis et al. Presented at DDW. 2022.

Vedolizumab Intravenous is Effective Across Multiple Treatment Targets in Chronic Pouchitis
EARNEST Trial

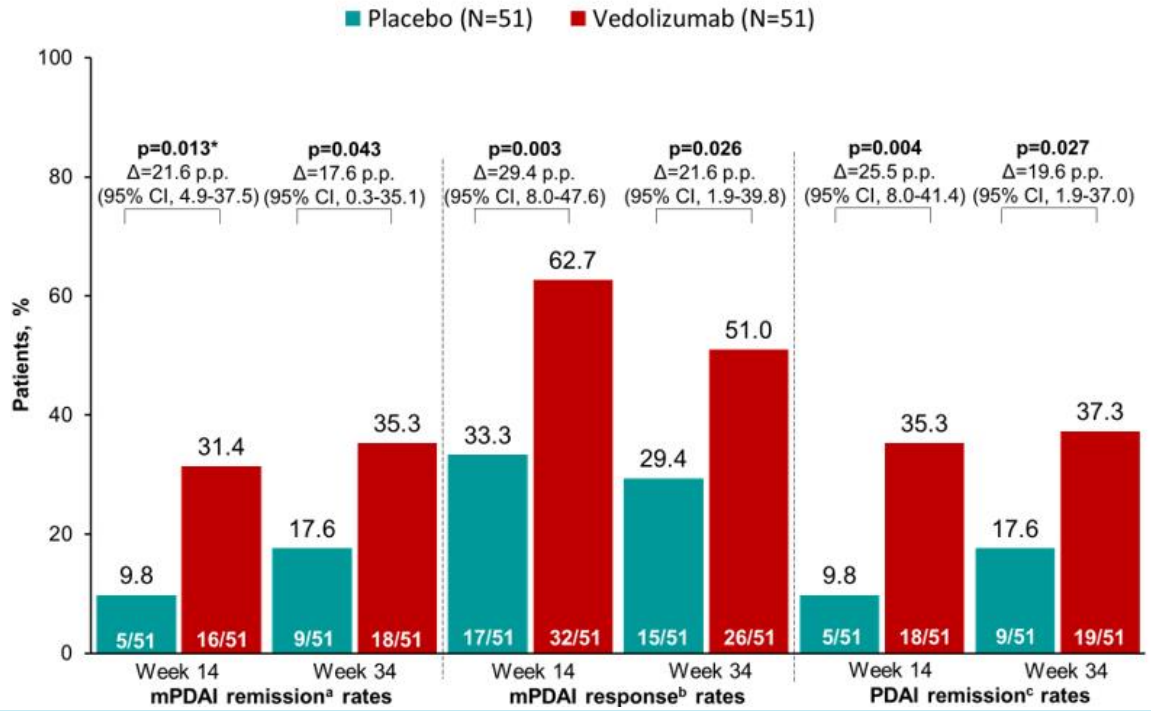
- Primary endpoint:
  - Clinically relevant remission defined as mPDAI < 5 and a reduction of mPDAI score > 2 points from baseline at week 14

- Secondary endpoints:
  - Clinically relevant remission defined as mPDAI < 5 and a reduction of mPDAI score > 2 points from baseline at week 34
  - Time to PDAI remission
  - mPDAI response at weeks 13 and 34
  - Change from baseline in PDAI endoscopic and histologic inflammation sub-score at weeks 14 and 34

Travis et al. Presented at DDW. 2022.

Vedolizumab Intravenous is Effective Across Multiple Treatment Targets in Chronic Pouchitis
EARNEST Trial

- 102 patients were treated, 51 per group
- Significant differences in favor of vedolizumab over placebo were seen in mPDAI remission rates, mPDAI response rates, and PDAI remission rates



Travis et al. Presented at DDW. 2022.

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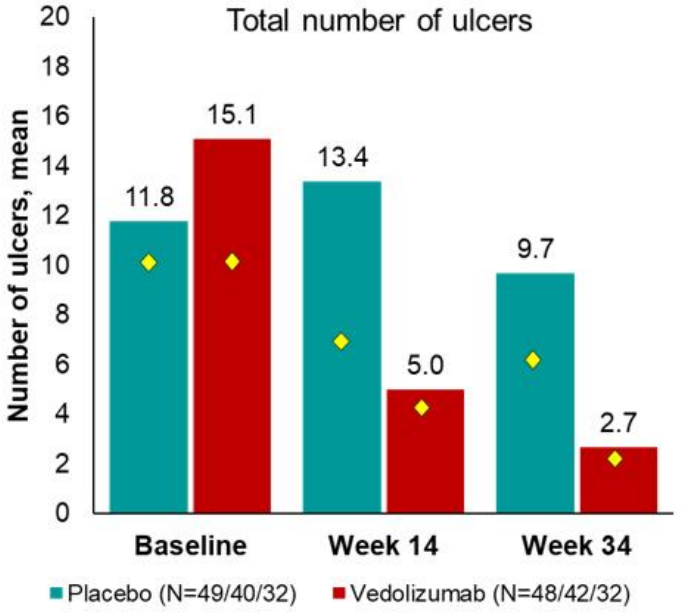
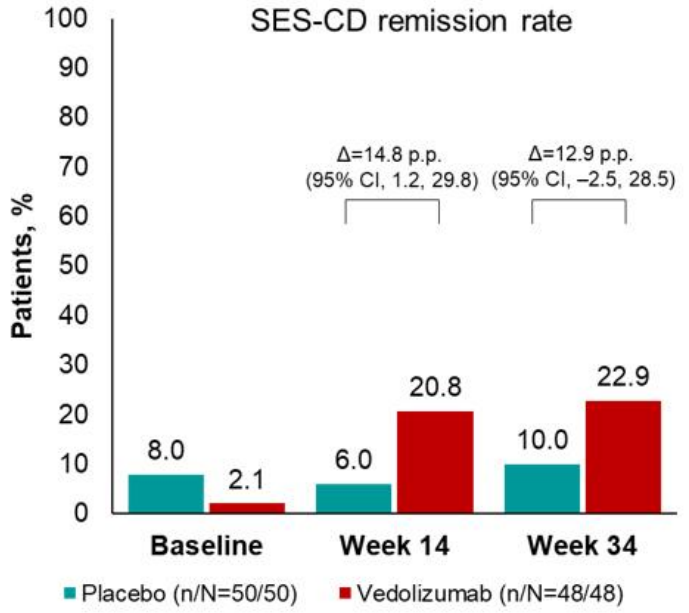
- Greater reduction in number of endoscopic ulcers from baseline for vedolizumab over placebo at weeks 14 and 34
- Higher proportion of patients in the vedolizumab vs placebo group had an improved SES-CD score and achieved SES-CD remission





Travis et al. Presented at DDW. 2022.

Vedolizumab Intravenous is Effective Across Multiple Treatment Targets in Chronic Pouchitis
EARNEST Trial

- Conclusions:
  - First and largest randomized, double-blind placebo-controlled trial of biologic therapy to show significant benefits across multiple treatment outcomes in patients with chronic pouchitis
  - Vedolizumab showed consistent treatment benefits over placebo across clinical, endoscopic, and histologic endpoints together with safety consistent with its established profile

Travis et al. Presented at DDW. 2022.

Efficacy and Safety of Extended Induction Treatment with Upadacitinib in Patients with Moderate-Severe UC

- Background:
  - Upadacitinib is a selective Janus kinase inhibitor and has been shown to safe and effective when administered at a dose of 45 mg once daily as 8-week induction therapy in moderate-severe UC
    - Significantly improves UC symptoms as early as day 1
    - Patients who achieve early symptom improvement are more likely to attain clinical remission or response at week 8
- Aim:
  - To evaluate the outcomes following extended induction (45 mg once daily for 16 weeks) followed by maintenance (15 or 30 mg once daily) treatment with upadacitinib in patients with UC who did not achieve a clinical response after 8 weeks induction

Vermeire et al. Presented at DDW. 2022.

Efficacy and Safety of Extended Induction Treatment with Upadacitinib in Patients with Moderate-Severe UC

- Methods:
  - Post-hoc analysis of U-ACHIEVE AND U-ACCOMPLISH studies
  - Patients with moderate-to-severe UC who failed to achieve a clinical response to 8 weeks induction treatment with upadacitinib 45 mg daily continued to receive 45 mg daily in an 8-week open-label extension
    - Clinical response defined as adapted Mayo score decrease >2 points and >30% from baseline, plus >1 point decrease in rectal bleeding score or absolute rectal bleeding score<1)
- Primary endpoint:
  - Efficacy at week 16 and week 52

Vermeire et al. Presented at DDW. 2022.

Efficacy and Safety of Extended Induction Treatment with Upadacitinib in Patients with Moderate-Severe UC

- Results:
  - 125 patients who failed to achieve a clinical response after 8 weeks of induction treatment received open-label upadacitinib 45 mg daily for an additional 8 weeks
  - 48.3% achieved a clinical response at week 16 and were re-randomized to upadacitinib 30 or 15 mg
  - Among responders at week 16, upadacitinib 30 mg vs 15 mg achieved the following endpoints at week 52:
    - Clinical remission – 33.3% vs 19.0%
    - Maintenance of clinical response – 66.7% vs 35.7%
    - Endoscopic improvement – 37.5% vs 23.8%

Vermeire et al. Presented at DDW. 2022.

Efficacy and Safety of Extended Induction Treatment with Upadacitinib in Patients with Moderate-Severe UC

	Patients, %		
	UPA 45 mg QD at Week 16 (induction) (N=125[a])	UPA 15 mg QD at Week 52 (maintenance)[b] (N=21)	UPA 30 mg QD at Week 52 (maintenance)[b] (N=24)
Clinical remission[c]	5.6	19.0	33.3
Clinical response[d]	48.3	(N=14) 35.7	(N=21) 66.7
No abdominal pain	40.0	38.1	41.7
No bowel urgency	30.4	28.6	41.7
Endoscopic improvement[e]	14.3	23.8	37.5
Endoscopic remission[f]	4.9	4.8	12.5
Histological–endoscopic mucosal improvement[g]	11.0	9.5	25.0
Histological improvement[h]	39.6	NE	NE
Mucosal healing[i]	3.4	4.8	8.3
Clinical remission[c] among patients who achieved clinical remission at the end of induction	NA	(N=1) 0	(N=2) 100
Clinical remission[c] and CS-free for ≥90 days immediately prior to Week 52 among patients who achieved clinical remission at the end of induction	NA	(N=1) 0	(N=2) 100
Endoscopic improvement[e] among patients who achieved endoscopic improvement at the end of induction	NA	(N=4) 25.0	(N=6) 50.0
Change from baseline in IBDQ total score (LS mean)	(N=104) 46.0	42.6	43.5
Change from baseline in FACIT-F score (LS mean)	(N=102) 8.7	9.0	10.6

Vermeire et al. Presented at DDW. 2022.

Efficacy and Safety of Extended Induction Treatment with Upadacitinib in Patients with Moderate-Severe UC

- Conclusions:
  - Prolonged induction treatment for a total of 16 weeks was beneficial in almost half of patients with UC who failed to achieve a clinical response after 8 weeks induction with upadacitinib 45 mg daily
  - Benefit of maintenance therapy in delayed responders was further demonstrated, with upadacitinib 30 mg daily providing greater benefit than upadacitinib 15 mg daily

Vermeire et al. Presented at DDW. 2022.

Conclusions

- Infliximab withdrawal, but not anti-metabolite withdrawal, was associated with a significantly higher risk of relapse than continuation of combination therapy
    - Almost all patients who discontinued infliximab achieved rapid remission when treatment was resumed
- Vedolizumab showed consistent benefits over placebo across clinical, endoscopic, and histologic endpoints in patients with chronic pouchitis
- Prolonged induction treatment with upadacitinib for a total of 16 weeks may capture response in patients with UC who failed to achieve a clinical response after 8 weeks induction