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Systematic review with meta-analysis: safety and tolerability of immune checkpoint inhibitors in patients with pre-existing inflammatory bowel diseases

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Summary

Background: Immune checkpoint inhibitors may variably impact patients with pre-existing autoimmune diseases.

Aims: To evaluate the risks and outcomes of adverse events in patients with pre-existing inflammatory bowel diseases treated with immune checkpoint inhibitors.

Methods: Through a systematic literature review up until July 31, 2020, we identified 12 studies reporting the impact of immune checkpoint inhibitors in 193 patients with inflammatory bowel disease. Outcomes of interest were relapse of inflammatory bowel disease, need for corticosteroids and/or biologics to manage inflammatory bowel disease relapse, and discontinuation of immune checkpoint inhibitors. We calculated pooled rates (with 95% confidence intervals [CI]) using random effects meta-analysis, and examined risk factors associated with adverse outcomes through qualitative synthesis of individual studies.

Results: On meta-analysis, 40% patients (95% CI, 26%-55%) experienced relapse of inflammatory bowel disease with immune checkpoint inhibitors. Among patients who experienced relapse, 76% (95% CI, 65%-85%) required corticosteroids, and 37% (95% CI, 22%-53%) required biologic therapy. Overall, 35% patients (95% CI, 17%-57%) with inflammatory bowel disease discontinued immune checkpoint inhibitors. Gastrointestinal perforation and abdominal surgery due to immune checkpoint inhibitor complications occurred in <5% patients. In a large study, inhibitors of cytotoxic T-lymphocyte antigen-4 (CTLA-4) were associated with a higher risk of relapse than programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors.

Conclusions: Approximately 40% of patients with pre-existing inflammatory bowel diseases experience relapse with immune checkpoint inhibitors, with most relapsing patients requiring corticosteroids and one-third requiring biologics. CTLA-4 inhibitors may be associated with higher risk of relapse.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Immune checkpoint inhibitors have become integral to the management of several advanced cancers.[1] By blocking inhibitory cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death 1 (PD-1), and programmed death ligand 1 (PD-L1), immune checkpoint inhibitors target mechanisms by which cancer cells evade cytotoxic T-lymphocyte activity. The removal of a physiologic braking system allows for upregulation of the adaptive cellular immune system, which leads to anti-tumour efficacy, but also promotes various immune-related adverse events (irAEs), involving the gastrointestinal tract, liver, joints, lungs, skin and endocrine glands.[2,3] Gastrointestinal irAEs are among the most frequent and severe, with colitis reported in 1%-14% of patients.[4]

Patients with pre-existing autoimmune diseases are typically excluded from clinical trials of immune checkpoint inhibitors. Recent observational studies suggest that patients with autoimmune diseases may be at higher risk of irAEs with immune checkpoint inhibitors,[5] although data on patients with inflammatory bowel diseases (IBD) are sparse. To inform safety of immune checkpoint inhibitors in patients with IBD, we conducted a systematic review with meta-analysis of cohort studies reporting rate, risk factors, and outcomes of relapse with immune checkpoint inhibitors in patients with IBD. As the prevalence of IBD increases in older adults, and the frequency of immune checkpoint inhibitor use increases in patients with cancer, this systematic synthesis will inform clinical practice and identify key knowledge gaps.

2 | METHODS

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards and followed an a priori protocol (available upon request).[6]

2.1 | Selection criteria

Studies included in this meta-analysis search were randomized controlled trials, cohort studies and case series that met the following inclusion criteria: (a) Patients: adults with established IBD and cancer, (b) Exposed to: approved immune checkpoint inhibitors (inhibitors of CTLA-4: ipilimumab, tremelimumab; PD-1: pembrolizumab, nivolumab; PD-L1: atezolizumab, durvalumab, avelumab), and reporting (c) Outcomes: rate and/or risk factors for flare of pre-existing IBD, need for corticosteroids and/or immunosuppressive therapy for management of flare, and complications of gastrointestinal perforation and abdominal surgery. We excluded studies that (a) included <5 patients with autoimmune diseases (to minimize selection bias), or (b) did not report outcomes separately for patients with IBD. From studies that combined patients with different autoimmune diseases together, we selectively abstracted data for patients with IBD (even if number of patients with IBD was <5 in those studies). We carefully excluded studies with the overlap of patients, when multiple studies reported from the same cohort of patients, we included data from the more comprehensive report.

2.2 | Search strategy

We updated a prior systematic review published in 2018 on the use of immune checkpoint inhibitors in the management of patients with cancer and pre-existing autoimmune diseases.[5] Briefly, this review identified 123 patients with pre-existing autoimmune diseases who were treated with immune checkpoint inhibitors (nine patients with IBD), from 49 publications. There was moderate confidence in the results of this review based on AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews-2).[7] We conducted a comprehensive search of PubMed, Embase and Cochrane Database of Systematic Reviews from January 1, 2017 to May 31, 2020. The search strategy combined the keywords and MeSH terms: ("immune checkpoint inhibitors" OR “nivolumab” OR “ipilimumab” OR “pembrolizumab” OR “atezolizumab” OR “durvalumab” OR “avelumab” OR "anti-PD1" OR "anti-PD-1" OR "anti-CTLA4" OR "anti-CTLA-4" OR "Immunotherapy") AND ("immune related adverse event" OR “adverse event” OR "colitis" OR "enteritis"). Two study investigators (AF, SS) independently reviewed the title and abstract of studies identified in the search, to exclude studies that did not address the research question of interest, based on prespecified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Conflicts in study selection at this stage were resolved by consensus, referring to the original article in consultation with a third reviewer (JM). Second, we performed a recursive search of the bibliographies of these selected articles as well as published systematic reviews on this topic, to identify any additional studies. Third, we conducted a manual search of abstracts from major gastroenterology and oncology conferences (Digestive Disease Week, United European Gastroenterology Week, Meeting of the American Society of Clinical Oncology) from 2018 to 2020 to identify additional abstracts on the topic.

2.3 | Data abstraction and risk of bias assessment

Two authors independently (JM, AF) abstracted data using a standardized data collection form: (a) study characteristics – primary author, time period of study/year of publication, geographic location; (b) patient characteristics – age, sex, smoking, body mass index, IBD type, IBD disease activity, prior IBD-related surgeries, treatment of IBD prior to initiation of immune checkpoint inhibitor, type of cancer, type of immune checkpoint inhibitor; (c) outcome assessment – proportion of patients with relapse of IBD, need for corticosteroids and/or biologics for managing flare, need for IBD-related surgery, IBD-related complications including

gastrointestinal perforation; as well as risk factors associated with adverse IBD outcome after exposure to immune checkpoint inhibitors. If outcomes were reported separately by type of immune checkpoint inhibitor, type of IBD (Crohn's disease or ulcerative colitis), or IBD disease activity at the time of immune checkpoint inhibitor initiation, it was abstracted separately. Any discrepancies were addressed by a joint re-evaluation of the original article, in consultation with a third reviewer (SS). Risk of bias in included studies was assessed using National Institute of Clinical Excellence (NICE) quality assessment for case series checklist.[8] We classified low risk of bias as studies which received maximum score, and moderate risk of bias for studies which score >4.

2.4 | Outcomes assessed

The primary outcome was proportion of patients with relapse of IBD in patients with pre-existing IBD exposed to immune checkpoint inhibitors. Since it was difficult to distinguish gastrointestinal irAEs vs relapse of IBD, both of these were combined into a single outcome and reported as relapse. Due to limited data on time period of follow-up for all patients, incidence rate of relapse could not be calculated.

Secondary outcomes were: (a) proportion of patients needing corticosteroids for management of flare of IBD (denominator was only patients with relapse of IBD), (b) proportion of patients needing biologic therapy for management of flare of IBD (denominator was only patients with relapse of IBD), (c) progression to gastrointestinal surgery, and/or development of gastrointestinal perforation, and (d) rate of discontinuation of immune checkpoint inhibitors in all patients with IBD. Risk factors associated with flare were inconsistently reported and synthesized qualitatively. We planned subgroup analyses to evaluate rates of outcome by type of immune checkpoint inhibitor, type of IBD, and IBD disease activity at time of immune checkpoint inhibitor initiation.

2.5 | Statistical analysis

We used double arcsine transformation described by Stuart and Ord to calculate standardized proportions (and 95% confidence interval [CI]) followed by the random-effects meta-analysis of proportions described by DerSimonian and Laird to calculate pooled rates (and 95% confidence interval [CI]) of relapse of IBD, need for corticosteroids and/or biologic therapy, and discontinuation of ICI.[9,10] We assessed heterogeneity between study-specific estimates using the inconsistency index (I^2), and used cut-offs of 0%-40%, 30%-60%, 50%-90% and 75%-100% to suggest minimal, moderate, substantial and considerable heterogeneity, respectively.[11] Small study effects (publication bias) was assessed visually using funnel plots, and statistically using Egger's regression test.[12] All analyses were performed using Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, NJ).

2.6 | Data availability statement

The data underlying this article are available within the article. All data were obtained from previously published studies in public domain.

3 | RESULTS

From a total of 767 unique studies identified using the search strategy, we included 11 new cohort studies, and additionally included nine patients with IBD from a previously published systematic review, for a total of 193 patients with pre-existing IBD treated with immune checkpoint inhibitors (Figure 1).[5,13-23]

3.1 | Characteristics and quality of included studies

Table 1 describes the baseline characteristics of patients included in the studies. Approximately 50% patients were treated for immune checkpoint inhibitors for melanoma. One hundred forty-nine patients were treated with PD-1 or PD-L1 inhibitors, 22 with CTLA-4 inhibitors, and 22 were treated with a combination of the two. Approximately 47% had underlying Crohn's disease, and 49% had ulcerative colitis. Average median time to follow-up was 15 months in nine studies reporting this. Of eight studies reporting IBD disease activity (n = 172 patients), 31 (18%) had clinically active disease at the time of initiation of immune checkpoint inhibitor.[5,14-16,19,21-23] Of five studies reporting IBD therapy at time of immune checkpoint inhibitor initiation (n = 151), 62 (41%) were not on any IBD-directed therapy and 51 (34%) were on 5-aminosalicylates; only 12 (8%) patients were on biologics.[5,14,15,22,23] Overall, the studies were at moderate risk of bias, with all studies being retrospective and occurring at tertiary or specialized centres. Table S1 details the detailed risk of bias assessment of included studies.

3.2 | Relapse of inflammatory bowel diseases

Of 193 patients, risk of relapse of IBD in individual studies ranged from 0% to 89%. On meta-analysis of 12 studies, 39.8% patients (95% CI, 26.1-54.5) experienced relapse of IBD (Figure 2), with substantial heterogeneity (I^2 = 66%).[5,13-23] Where reported, range of median time to relapse was 2-5 months after initiation of immune checkpoint inhibitors. Data were insufficient to perform subgroup analyses based on type of immune checkpoint inhibitor, type of IBD, and IBD disease activity at baseline.

3.3 | Need for corticosteroids to manage IBD flare

Of 10 studies in which patients with IBD experienced relapse, seven studies reported subsequent treatment of relapsing IBD.[5,14-16,20,22,23]

Of 68 patients experiencing relapse of IBD, 52 needed corticosteroids (range in individual studies, 50%-100%). On meta-analysis, 76.1% patients (95% CI, 65.4-85.4) with relapse of IBD after exposure to immune checkpoint inhibitors required corticosteroids, with minimal heterogeneity (I^2 = 1%) (Figure 3).

3.4 | Need for biologic agents to manage IBD flare

In six studies reporting relapse of IBD after exposure to immune checkpoint inhibitors (n = 67), 23 patients required initiation of biologic agents for management of IBD.[5,14-16,22,23] On meta-analysis, 36.6% of patients (95% CI, 21.9-52.7) with flare of IBD required biologic agents, with minimal heterogeneity (I^2 = 27%) (Figure 4). Of 176 patients with IBD treated with immune checkpoint inhibitors (regardless of whether they experienced flare of IBD), 16.1% (95% CI, 8.5-28.3) required biologic agents for managing IBD, with moderate heterogeneity (I^2 = 42%).

3.5 | Discontinuation of immune checkpoint inhibitors

In eight studies reporting discontinuation of immune checkpoint inhibitors (n = 173), 82 patients with pre-existing IBD with cancer discontinued immune checkpoint inhibitor.[5,13-17,20,23] On meta-analysis, 35.4% patients (95% CI, 16.8-56.7) discontinued immune checkpoint inhibitor, with considerable heterogeneity (I^2 = 82%) (Figure 5).

3.6 | Other outcomes

Progression to abdominal surgery was infrequently reported; in three studies reporting this outcome, 3/124 (2.4%) required abdominal surgery due to refractory flare of IBD.[14,15,23] In three studies, 6/120 patients (5%) experienced gastrointestinal perforation.[13,15,23] Mortality was incompletely reported, but in one of the largest retrospective studies, no deaths were reported due to gastrointestinal irAE in 42 patients with IBD treated with immune checkpoint inhibitor.[15]

3.7 | Risk factors for adverse IBD-related outcomes

There were limited data on predictors of IBD relapse with immune checkpoint inhibitor therapy. In the largest retrospective analysis included in this meta-analysis, inhibition of CTLA-4 was associated with increased risk of gastrointestinal irAEs on univariate analysis (OR, 3.19; 95% CI, 1.8-9.48), with a similar trend

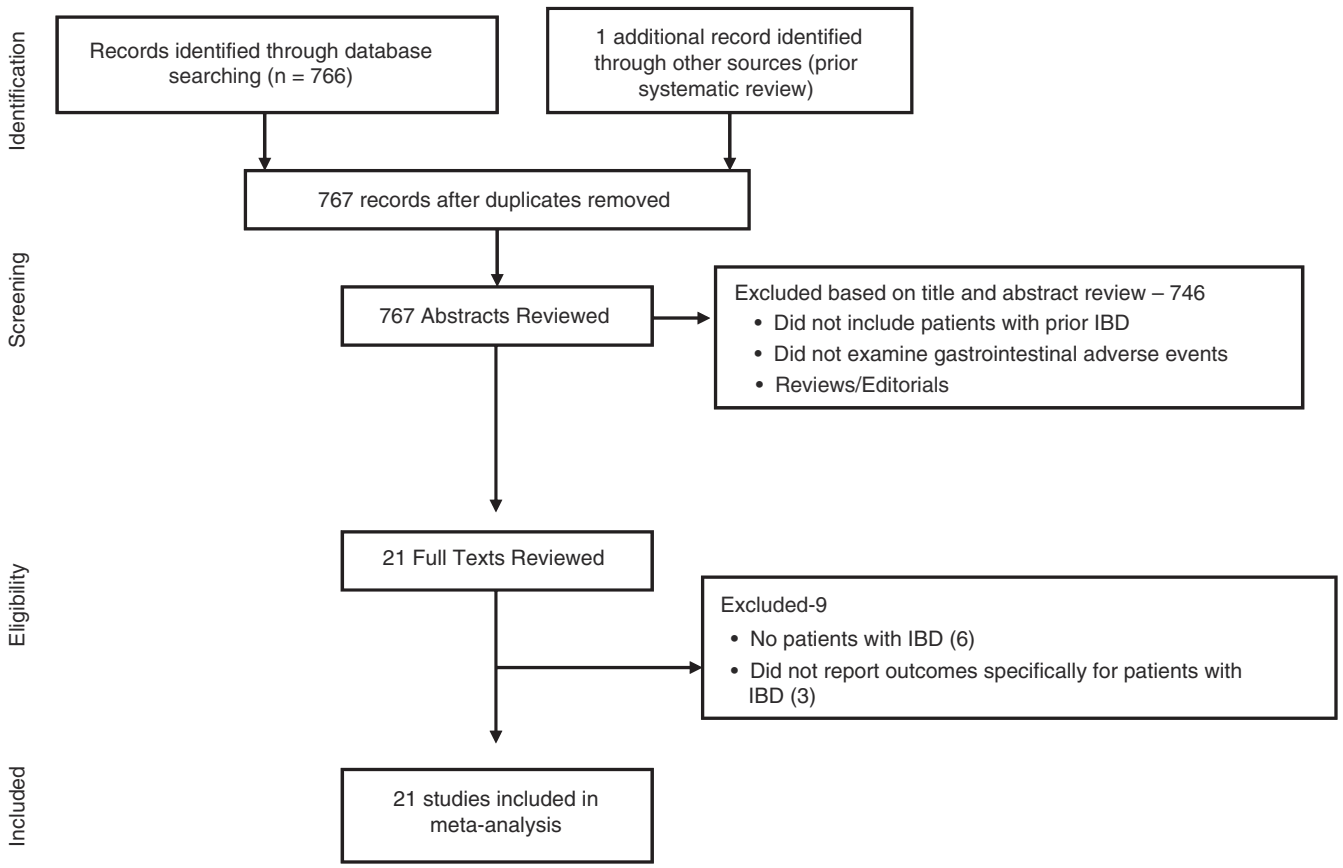

FIGURE 1 Study selection flowchart

TABLE 1 Characteristics of patients with pre-existing IBD treated with immune checkpoint inhibitors for cancer

	Abdel-Wahab[5] 2018	AbuSbeih[15] 2018	Leonardi[19] 2018	Kahler[20] 2018	Cortellini[18] 2019	Grover[23] 2020	Johnson[22] 2016	Kaur[17] 2019	Menzies[21] 2017	Tison[16] 2019	Braga Neto[14] 2020	Brown[13] 2020
Age, median (IQR)	52 (49-60)	65 (54-74)	67 (45-90)[a]	61 (34-78)[a]	69 (24-92)[a]	68 (36-84)	60 (30-80)[a]	64 (53-72)[a]	71 (23-88)[a]	65 (45-89)[a]	CD: 65 (62-72) UC: 56 (53-71)	–
Sex (male, %)	56%	68%	38%[a]	44%[a]	66%[a]	36%	57%[a]	67%[a]	60%[a]	57%[a]	54%	–
Cancer Type (N)												
Melanoma	6	45	0	3	–	–	6	–	5	8	7	9
Lung	2	23	6	0	–	–	0	–	0	6	0	0
Other	1	34	0	0	–	–	0	–	0	0	6	0
Type of Immune Checkpoint Inhibitor (ICI) (N)												
PD1/PDL1	4	85	6	0	3	19	0	2	5	13	12	0
CTLA-4	5	7	0	3	0	0	6	0	0	1	0	0
Combination	0	10	0	0	0	2	0	0	0	0	1	9
IBD history												
CD	4	49	3	1	3	10	3	0	3	6	5	–
UC	5	49	3	2	0	9	3	1	2	8	8	–
IC	0	4	0	0	0	2	0	1	0	0	0	–
Prior IBD Surgery	2	28	–	–	–	9	4	–	2	–	–	–
Active IBD	4	16	1	–	–	3	2	–	0	1	4	–
IBD treatment at time of ICI initiation												
None	2	43	–	–	–	11	0	–	–		6	–
5-ASA	0	37	–	–	–	7	2	–	–	–	5	–
IMM	0	4	–	–	–	0	0	–	–	–	1	–
Biologic	0	9	–	–	–	2	0	–	–	–	1	–

Abbreviations: 5ASA, 5-aminosalicylic acid; CD, Crohn's disease; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IBD, inflammatory bowel disease; IC, indeterminate colitis; ICI, immune checkpoint inhibitor; IMM, immunomodulator; IQR, interquartile range; PD1, programmed cell death protein 1; PDL1, Programmed cell death-ligand 1; UC = ulcerative colitis.

[a]Average from study population, not IBD patients only (unavailable); of note, four patients overlapped between the cohorts of Johnson 2016[22] and Abdel-Wahab 2018.[5] These four patients were included in Johnson 2016[22] and excluded from Abdel-Wahab 2018[5] in the table above and in overall analysis.

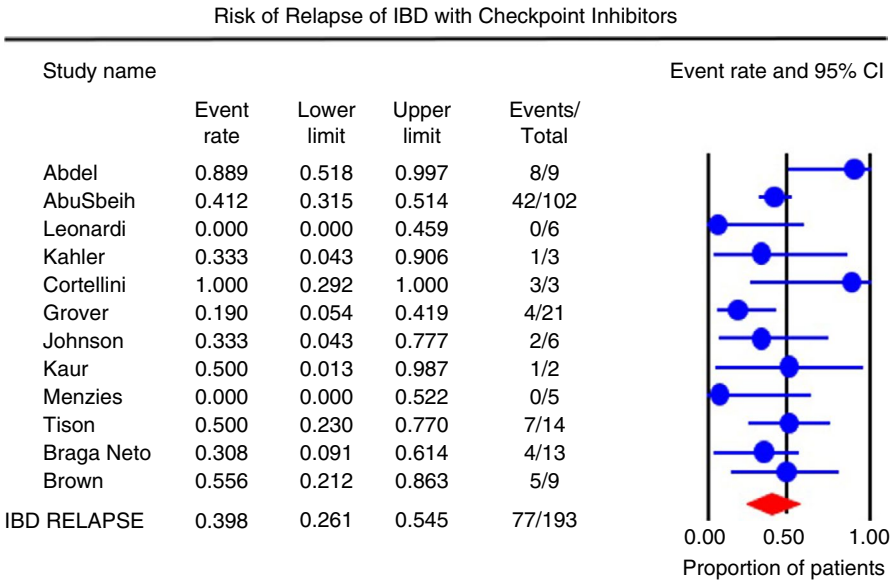

FIGURE 2 Pooled rate (and 95% confidence interval) of relapse of IBD after initiation of treatment with immune checkpoint inhibitor, using double arcsine transformation, based on 12 studies with 193 patients

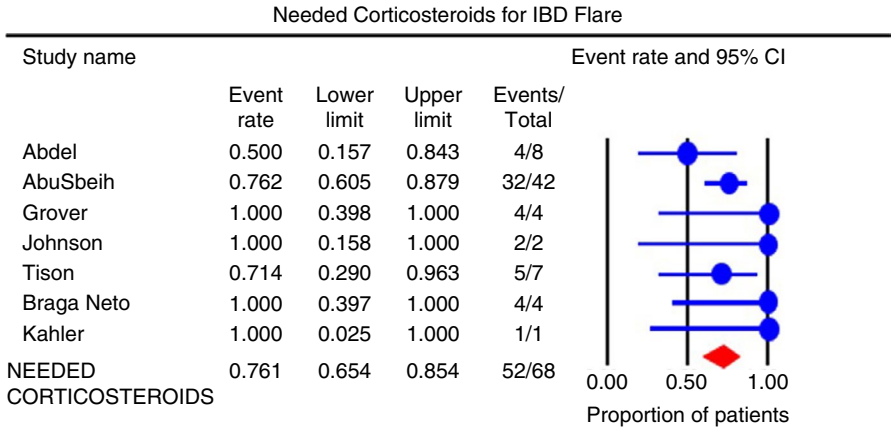

FIGURE 3 Pooled rate (and 95% confidence interval) of need for corticosteroids in patients with IBD experiencing relapse after initiation of treatment with immune checkpoint inhibitor, using double arcsine transformation, based on six studies with 68 patients

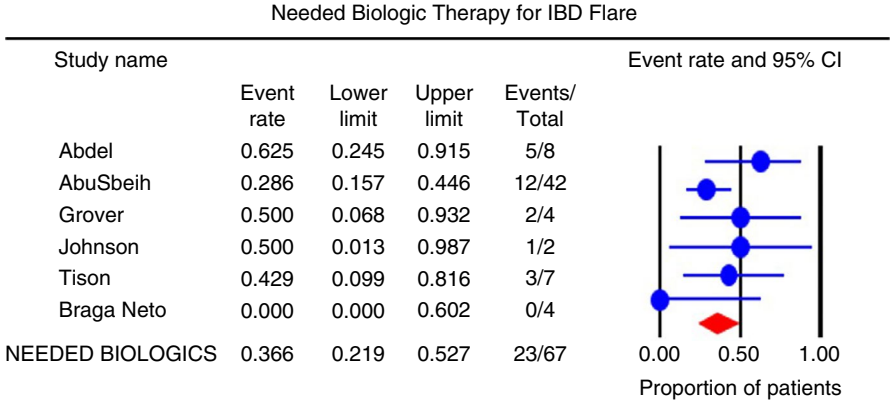

FIGURE 4 Pooled rate (and 95% confidence interval) of need for biologics in patients with IBD experiencing relapse after initiation of treatment with immune checkpoint inhibitor, using double arcsine transformation based on six studies with 67 patients

on multivariate analysis (OR, 4.72; 95% CI, 0.95-23.53).[15] Active IBD at time of immune checkpoint inhibitor therapy, being on IBD-related immunosuppressive therapy, or endoscopic severity of IBD were not associated with risk of relapse. Grover and colleagues observed that a higher rate of IBD relapse in patients treated with combination of inhibitors of ipilimumab and nivolimumab, and lower risk of relapse in patients treated with inhibitors of PD-1/PD-L1. Patients who experienced IBD relapse, were less likely to be on IBD-related therapy at time of immune checkpoint inhibitor initiation (17% vs. 50%, $P = 0.17$).

3.8 | Publication bias

No evidence of small study effects was observed for the primary outcome of risk of relapse based on Egger's test ($P = 0.99$).

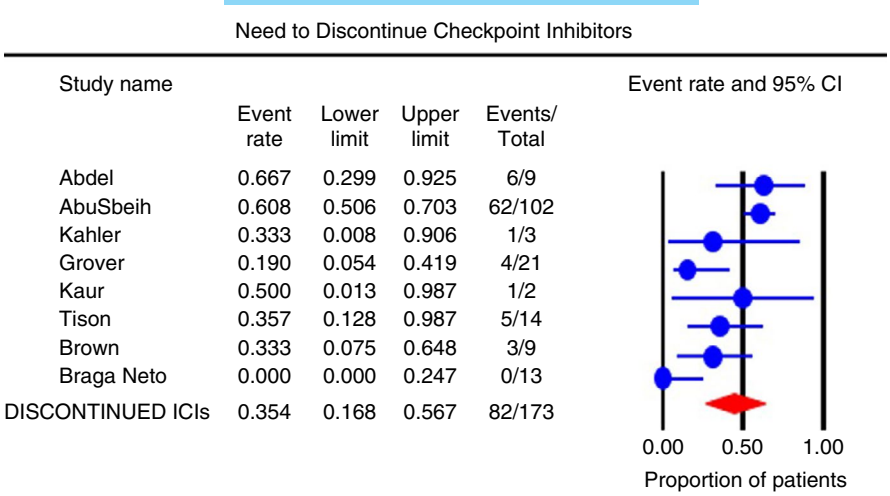

FIGURE 5 Pooled rate (and 95% confidence interval) of need to discontinue immune checkpoint inhibitor in patients with pre-existing IBD, using double arcsine transformation, based on eight studies with 173 patients

4 | DISCUSSION

As the prevalence of IBD in older patients increases, and immunotherapy becomes an integral component of cancer therapy, an increasing proportion of patients with IBD who develop cancer will be treated with immune checkpoint inhibitors. To evaluate safety of immune checkpoint inhibitor in patients with pre-existing IBD, we conducted a systematic review and meta-analysis with 193 immune checkpoint inhibitor-treated patients with IBD and made several important observations. Approximately 40% patients with pre-existing IBD experienced relapse of their IBD on initiation of immune checkpoint inhibitors. Unfortunately, the studies included for meta-analysis did not include a comparator group of patients with IBD who were not exposed to immune checkpoint inhibitors. The annual risk of relapse in patients with IBD in clinical remission is estimated to be ~20% and it is important to note that some cases of diarrhoea or colitis may have been due to the natural course of IBD; though it is not currently possible to differentiate these aetiologies.

Of those developing IBD relapse, approximately 76% required corticosteroids for managing their flare, and 37% required biologic therapy after failure of corticosteroids. Risk of gastrointestinal perforation and abdominal surgery was <5%. Although significant inter-study reporting heterogeneity did not allow for meta-analysis or meta-regression of risk factors, qualitative analysis of one of the largest studies suggests that patients treated with inhibitors of CTLA-4 may have higher risk of IBD relapse as compared to PD1/PDL1 inhibition.[14] Approximately 35% patients with IBD discontinued immune checkpoint inhibitor therapy prematurely. In comparison, 6.8%-7.9% of 8863 patients in clinical trials developed severe immune-related diarrhoea or colitis that would necessitate discontinuation of therapy.[24] These findings suggest that although the rate of gastrointestinal irAEs with immune checkpoint inhibitor therapy in patients with IBD is higher than patients without pre-existing IBD, most of these relapses are manageable with corticosteroids or biologic therapy, and are associated with low rate of complications and abdominal surgery.

Approximately 10%-50% patients treated with immune checkpoint inhibitor experience diarrhoea, and 1%-15% experience colitis in clinical trials, with higher rates observed in patients treated with inhibitors of CTLA-4.[2,4] Corticosteroids are recommended for patients with grade 2 or higher severity of symptoms, and biologic therapy is reserved for a smaller set of patients who are refractory to corticosteroids. In a large single centre experience of gastrointestinal irAEs with immune checkpoint inhibitor therapy in 327 patients without pre-existing IBD, Yang and colleagues observed gastrointestinal irAEs in 36% patients, of whom 38% required corticosteroids.[25] Our findings in patients with pre-existing IBD suggest a higher rate of relapse, particularly more severe relapse since 76% required corticosteroids. In a previous systematic review of 123 patients with any autoimmune disease treated with immune checkpoint inhibitors, Abdel-Wahab and colleagues had reported 75% patients may experience exacerbation of pre-existing autoimmune disease, irAEs, or both.[5] Approximately 62% were managed with corticosteroids, 16% required immunosuppressive therapy, and 17% required discontinuation of immune checkpoint inhibitor therapy.

Biologic therapy for management of gastrointestinal irAEs is recommended in patients with failure of corticosteroids.[26] In our review, roughly half the patients with flare of pre-existing IBD who received immune checkpoint inhibitors and were steroid-refractory, requiring escalation to biologic therapy. Infliximab was the most commonly used biologic agent. In two studies, vedolizumab was also used though effectiveness was not stratified by type of biologic agent.[15,23] In a cohort of immune checkpoint inhibitor-induced gastrointestinal irAEs who failed corticosteroids (n = 19) and infliximab (n = 9), Abu-Sbeih and colleagues reported outcomes with vedolizumab.[27] They observed that approximately 95% and 67% patients who escalated to vedolizumab after failure of corticosteroids, and failure of infliximab, experienced clinical success, respectively. Vedolizumab's gut-tropic mechanism of action without systemic immunosuppression in patients with advanced cancers make it a potentially attractive option for patients who experience IBD relapse with immune checkpoint inhibitors after failure of corticosteroids and/or infliximab. Other IBD-directed therapies such as tofacitinib has also been used in patients with immune-mediated colitis with success.[28]

We observed a considerably high rate of immune checkpoint inhibitor discontinuation, with approximately 35% patients with

pre-existing IBD discontinuing immune checkpoint inhibitors, regardless of IBD relapse or not. These rates of drug discontinuation are higher than those reported in clinical trials of immune checkpoint inhibitors, and higher than 17% reported risk of immune checkpoint inhibitor discontinuation in a systematic review combining all autoimmune diseases.[5] This high rate of treatment discontinuation may be related to paucity of data in this population to guide treatment decisions, and concern for complications such as perforation.

The strengths of our synthesis are the systematic review with well-defined inclusion and exclusion criteria, assessment of multiple clinically relevant outcomes, and attempted synthesis of risk factors for relapse based on qualitative assessment of individual studies. Our review was limited by paucity of underlying data with many small individual cohorts. Most of the included studies combined multiple autoimmune diseases, with limited IBD-specific data. We were unable to compare differential risk of relapse of IBD with inhibitors of CTLA-4 and PD-1/PD-L1, as has been observed for gastrointestinal irAEs in patients without pre-existing IBD.

In summary, approximately 40% patients with pre-existing IBD experience relapse of IBD (or gastrointestinal irAEs) on initiation of immune checkpoint inhibitors, at a higher rate and greater severity than patients without pre-existing IBD. Approximately three-fourth of the patients require corticosteroids for managing their flare, and roughly half of these require biologic therapy. Risk of gastrointestinal perforation and abdominal surgery was <5%. These findings can directly inform clinical practice when discussing use of immune checkpoint inhibitors in patients with pre-existing IBD. Future studies evaluating risk factors associated with severe relapse, and timing, type and duration of biologic therapy for managing IBD relapse in patients with IBD being treated with immune checkpoint inhibitors are warranted.

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AUTHORSHIP

Guarantor of the article: Siddharth Singh.

Author contributions: Study concept and design: AF, SS; Acquisition of data: JM, AF, SS; Analysis and interpretation of data: JM, SS; Drafting of the manuscript: JM, SS; Critical revision of the manuscript for important intellectual content: AF, AKH, VA, WJS.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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