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BRIEF REPORT

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Systematic review of TNFα-induced paradoxical psoriasis: Treatment outcomes of switching to alternative biologic therapies in inflammatory bowel disease patients

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ABSTRACT

Objectives: The objective of this systematic review was to evaluate the efficacies of different biologic therapies in treating tumor necrosis factor-alpha (TNFα)-induced paradoxical psoriasis (PXP) and controlling inflammatory bowel disease (IBD) symptoms.

Methods: We conducted a literature search of the Ovid EMBASE, Ovid Medline, Web of Science Core Collection, and Cochrane Central Register of Controlled Trials databases from their inception to October 3, 2021. We considered all peer-reviewed, randomized controlled trials, chart reviews, and observational studies that discussed the TNFα-induced PXP treatment outcomes in IBD patients of switching to different biologic therapies.

Results: Switching to ustekinumab (UST) resulted in complete or partial resolution of TNFα-induced PXP in 83.1% of patients (74 out of 89 patients), while switching to either vedolizumab (VDZ) or secukinumab led to complete resolution in 100% of patients (eight out of eight patients). Approximately 75.4% of patients who were switched to UST remained in IBD remission, 4.6% in partial remission, and 20.0% in the flare of IBD.

Conclusions: UST has sufficient data to demonstrate the efficacy in treating TNFα-induced PXP and controlling IBD symptoms concurrently. More data is needed to validate the efficacies of VDZ and SEC in treating TNFα-induced PXP in IBD patients.

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KEYWORDS
TNFα-induced psoriasis; paradoxical psoriasis; inflammatory bowel disease; biologics; ustekinumab

Introduction

Introduction of biologic therapies has transformed the way we manage inflammation in the gut and the skin. Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal (GI) tract. Over the past several decades, anti-tumor necrosis factor (anti-TNFα), such as infliximab (IFX) and adalimumab (ADA), has been the mainstay biologic therapy for these patients. However, with increasing utilization of anti-TNFα agents, paradoxical inflammation of the skin, specifically paradoxical psoriasis (PXP), has been reported in IBD patients (1). For these patients, switching to a different class of biologic therapies has been shown to successfully treat PXP as well as control GI symptoms (2). Here, we performed a systematic review to evaluate the efficacies of different biologic therapies in treating PXP and controlling symptoms of IBD.

Methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and using pre-defined search terms, we conducted electronic literature searches to identify relevant studies (RR, SW, and JSM) (Figure 1). We searched the following databases from their inception to the date of search on October 3, 2021: Ovid EMBASE, Ovid Medline, Web of Science Core Collection, and Cochrane Central Register of Controlled Trials. Key search terms included 'inflammatory bowel disease,' 'Crohn's disease,' 'ulcerative colitis,' 'tumor necrosis factor inhibitor,' 'psoriasis,' 'adverse reaction,' and specific biologics therapies (e.g. ustekinumab, vedolizumab, secukinumab, and others). The reference section of each eligible study was manually screened for potentially relevant studies. Our inclusion criteria were peer-reviewed, English-language articles that discussed the TNFα-induced PXP treatment outcomes in IBD patients of switching to alternative biologic therapies. Randomized controlled trials (RCTs), chart reviews, and observational studies (including case reports and case series) were considered. Review articles, basic research studies, and articles that did not meet the inclusion criteria were excluded. Three investigators (RR, HP, and JSM) initially assessed study eligibility by screening titles and abstracts, followed by three investigators (RR, MR, and JSM) reviewing full text for final study inclusion and data extraction. Any disagreement or data inconsistency were resolved by discussion. Included studies were assessed for methodological

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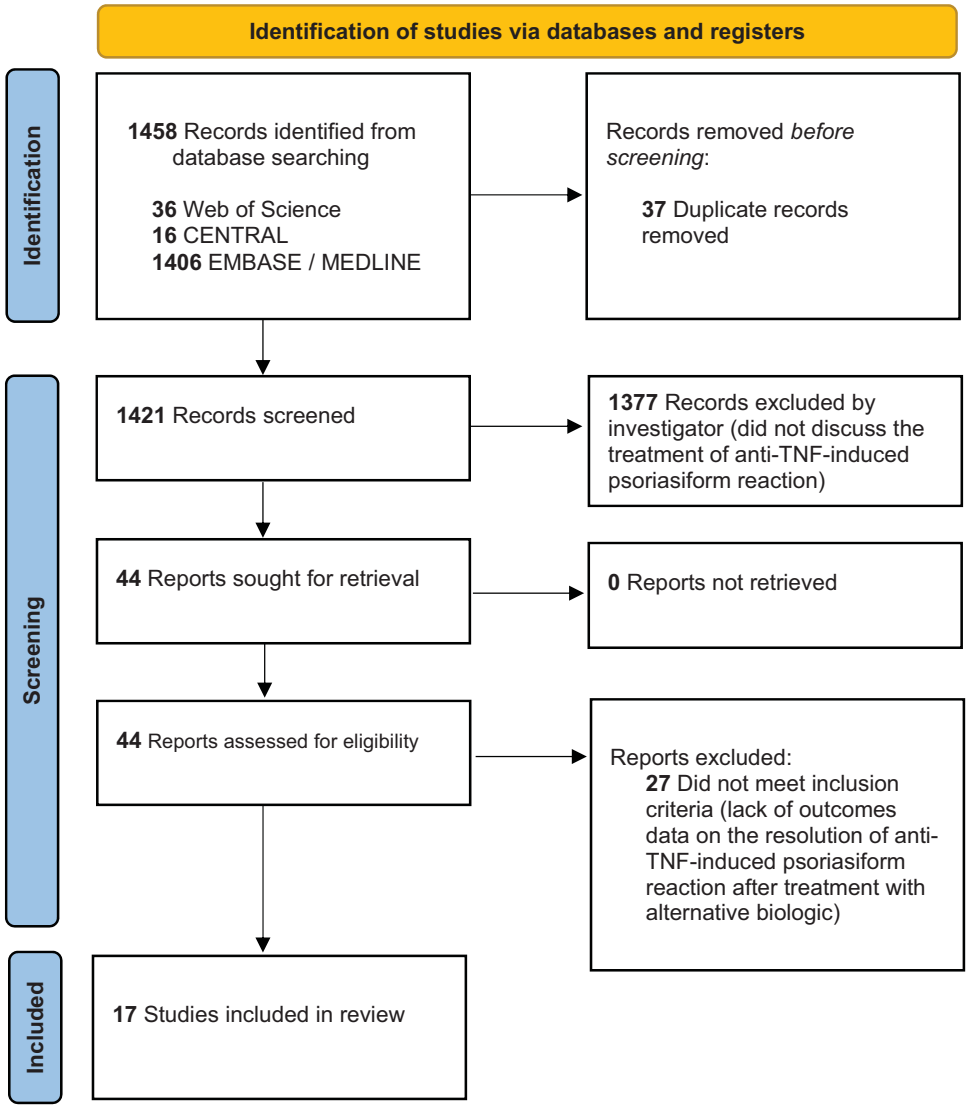

Figure 1. PRISMA flow diagram for systematic review. PRISMA: preferred reporting items for systematic reviews and meta-analyses.

Table 1. Quality appraisal of included studies.[a]

	Adequate description of IBD presentation	Accurate diagnosis of psoriasiform reaction	**Convincing evidence in support of psoriasiform reaction**	Alternate explanations were considered and refuted
Boggs et al. (5)	Yes	Yes	Yes	Yes
Dolinger et al. (6)	Yes	Yes	No	No
Eickstaedt et al. (7)	Yes	Partial	Yes	Yes
Ezzedine et al. (4)	Yes	Yes	Yes	Yes
George et al. (8)	Yes	Yes	Yes	Partial
Gold et al. (9)	Partial	Yes	Partial	No
Guerra et al. (10)	Yes	Yes	Yes	Partial
Hirsch et al. (11)	Yes	Yes	Yes	Yes
Kodama et al. (12)	Yes	Yes	Yes	Yes
Olbjorn et al. (13)	Yes	Yes	Yes	Partial
Pijls et al. (14)	Yes	Partial	Yes	Yes
Prieto et al. (15)	Partial	Yes	Partial	No
Pugliese et al. (16)	Yes	Yes	Yes	Yes
Sahuquillo-Torralba et al. (17)	Yes	Yes	Yes	Yes
Santos et al. (18)	Yes	Yes	Partial	No
Tillack et al. (1)	Yes	Yes	Yes	Yes
White et al. (19)	Yes	Yes	Yes	Partial

IBD: inflammatory bowel disease.
[a]Using modified criteria for systematic reviews involving case reports (3).

Table 2. Anti-TNF treatments most likely to lead to a psoriasiform reaction.

Anti-TNF inhibitor causing psoriasiform reactions (% out of all psoriasiform reactions reported in the included studies)					Switched to second anti-TNF after psoriasiform reaction	Improvement of anti-TNF psoriasiform reaction
ADA – 151/380 (39.7%)	**IFX – 222/380 (58.4%)**	**CZP – 6/380 (1.6%)**	**GOL – 0/380 (0%)**	**ETA – 1/380 (0.3%)**	**56/380**	**22/56 (39.2%)**

Anti-TNF: anti-tumor necrosis factor; ADA: adalimumab; IFX: infliximab; CZP: certolizumab pegol; GOL: golimumab; ETA: etanercept.

Table 3. Resolution of anti-TNF-induced psoriasiform reaction and status of IBD upon treatment with alternative biologic therapy.

Drug name	**Total cases, $n = 97$**	**Complete resolution of psoriasiform reaction** (%)	**Partial resolution of psoriasiform reaction** (%)	**No resolution** (%)	**Time (months) to resolution with new biologic treatment, mean (STDEV), $n = 56$**[a]	IBD data reported, $n = 70$	IBD remission	IBD partial	IBD flare
UST	89	64/89 (71.9%)	10/89 (11.2%)	15/89 (16.9%)	7.29 (5.94–8.64)	65/89	49/65 (75.4%)	3/65 (4.6%)	13/65 (20.0%)
VDZ	6	6/6 (100%)	0 (0%)	0 (0%)		5/6	4/5 (80.0%)	0 (0%)	1/5 (20.0%)
SEC	2	2/2 (100%)	0 (0%)	0 (0%)		0/2	N/A	N/A	N/A

Anti-TNF: anti-tumor necrosis factor; IBD: inflammatory bowel disease; UST: ustekinumab; VDZ: vedolizumab; SEC: secukinumab; N/A: not applicable.
[a]Time to resolution was reported in 56 out of 97 patients.

quality using the modified criteria for systematic reviews involving case reports (Table 1) (1,3–19).

Results

At the end of our screening process, we identified and included 17 studies in our final analysis (3 prospective cohort studies, 1 retrospective cohort study, 5 retrospective chart reviews, 1 case-control study, 3 case reports, and 4 case series) (Figure 1). Across all studies, there were 380 IBD patients who experienced PXP after initiation of anti-TNFα agents with 58.4% ($n = 222$) and 39.7% ($n = 151$), 1.6% ($n = 6$), 0.3% ($n = 1$), and 0% ($n = 0$) reporting IFX, ADA, CZP, ETA, and GOL as culprits, respectively (Table 2). Sixty-four out of 380 patients reported therapy duration with anti-TNFα agents before developing PXP with an average duration of 18.75 months. 56 out of 380 patients were subsequently switched to a different anti-TNFα agent, and only 39.2% of patients (22 out of 56) reported improvement in the skin (Table 2). When switching to a different class of biologic therapy, ustekinumab (UST) was the most common choice (89 out of 97 patients) (Table 3) (4). 83.1% of patients (74 out of 89) who were switched to UST experienced partial (10 out of 89) or complete resolution (64 out of 89) of PXP (Table 3). A much smaller subset of patients was switched to vedolizumab (VDZ) (6 out of 97) and secukinumab (SEC) (2 out of 97), but 100% of these patients experienced complete resolution (Table 3). 56 out of 97 patients reported time to resolution of PXP upon switching to a new biologic therapy (i.e. UST, VDZ, and SEC) with an average treatment duration of 7.29 months (Table 3). At the same time, disease status of IBD was reported in 70 out of 97 patients with 65 of 89 and 5 out of 6 for UST and VDZ, respectively (Table 3). After being switched to UST, 75.4% of patients remained in remission (49 out of 65), 4.6% in partial remission (3 out of 65), and 20.0% in flare of IBD (13 out of 65). After being switched to VDZ, 80.0% of patients remained in remission (4 out of 5) and 20.0% in flare of IBD (1 out of 5) (Table 3).

Discussion

In summary, our systematic review demonstrates that IFX and ADA are responsible for the majority of PXP reported in IBD patients treated with anti-TNFα agents, albeit CZP and GOL are without sufficient treatment data. Switching to UST results in complete or partial resolution of PXP in 83.1% of patients ($n = 89$), while switching to either VDZ or SEC led to complete resolution in 100% of patients ($n = 8$). However, more treatment data with VDZ and SEC is needed to determine if they are superior to UST. Additionally, switching to a different biologic therapy for the treatment of PXP should be considered in the context of IBD status. Switching to UST results in IBD flare in 20.0% of patients ($n = 65$). While switching to VDZ also results in IBD flare in 20.0% of patients ($n = 6$), treatment data is insufficient at this time to draw any conclusion. Our study was limited by lack of RCTs. However, it highlighted the need for continued investigation in this multidisciplinary field to evaluate the efficacies of available biologic therapies to develop evidence-based treatment algorithms for IBD patients suffering from TNFα-induced PXP.

Author contributions

JSM: concept of the study. RR, SW, and JSM: design of the study. RR, HP, MR, SW, and JSM: acquisition and analysis of data. RR and JSM: interpretation of data. RR, HP, and JSM: drafted the manuscript. RR and JSM: revised the manuscript. All authors approved the version to be published.

Disclosure statement

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