Review Article

Journal of Cutaneous Medicine and Surgery
2022, Vol. 26(4) 414–419

DOI: 10.1177/12034754221088556
journals.sagepub.com/home/cms

Canadian Dermatology Association
Association canadienne de dermatologie

A Systematic Review Characterizing Psoriatic Arthritis Onset and Exacerbation in Patients Receiving Biologic Therapy

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Abstract

Background: While biologic therapies revolutionized treatment of immune-mediated inflammatory diseases (IMIDs), some adverse effects have been noted. This includes the development and exacerbation of PsA in patients on biologic agents, however the outcomes were not extensively explored.

Objective: To perform a systematic review to characterize the outcomes of PsA onset or exacerbation secondary to biologic use.

Methods: MEDLINE and EMBASE search conducted on March 23, 2021 resulted in 18 studies comprised of 64 patients.

Results: Of the 64 patients, 57 (89.1%) experienced new-onset PsA and 7 (10.9%) experienced exacerbation of preexisting PsA following exposure to a biologic; most commonly a TNF-α inhibitor (42.2%, *n* = 27/64) and IL-12/23 inhibitors (39.1%, *n* = 25/64). The mean durations of biologic use before PsA onset and exacerbation were 14.8 months and 5.2 months, respectively. Twenty-four patients (44.4%) subsequently switched to an alternate biologic without further reports of PsA-related adverse events. All 64 patients reported a specific treatment for PsA; most commonly discontinuation of the associated biologic agent (32.8%, *n* = 21/64). Complete resolution of PsA was reported in 35.9% (*n* = 23/64) of cases, of which 91.3% (*n* = 21/23) resulted after discontinuation of biologic.

Conclusion: Although we characterized outcomes of PsA induction and exacerbation secondary to biologic use, large-scale studies are required.

Keywords

psoriatic arthritis, systematic review, biologics, paradoxical reaction

Introduction

Biologic therapies have revolutionized the treatment of immune-mediated inflammatory diseases (IMIDs) by targeting cytokine activity, specifically interleukins (IL) and tumor necrosis factor (TNF).[1] Although inhibiting proinflammatory cytokines can prevent disease progression, biologic use has been recently associated with the onset of paradoxical dermatologic adverse events.[2] In particular, several cases have reported an onset or exacerbation of psoriatic arthritis (PsA) following biologic treatment.[3,4]

PsA is a chronic, immune-mediated disease characterized by inflammation of the entheses and joints.[5] It has an incidence of approximately 6 per 100,000 per year, affecting men and women equally.[6] PsA is a multisystemic disease with immunological factors influencing its pathogenicity, including the expression of natural killer group 2 member (NKG2D) driven by IL-15.[7,8] Cytokine imbalance due to initiation of a biologic agent has been associated with PsA related joint inflammation.[9] Subsequent PsA onset can have

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a significant impact on one's quality of life due to associated comorbidities including osteoporosis, bowel inflammation, uveitis, and cardiovascular disease.[5,7]

Studies describing PsA secondary to biologic use are limited to individual case reports; thus, the clinical outcomes are not known with certainty. Currently, there is no summary of biologics that has been linked to PsA onset or exacerbation. The aim of this review is to summarize relevant reports of development of new-onset PsA or exacerbation of preexisting PsA in patients on biologics for IMIDs.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] Ethics board approval was waived due to the nature of the study.

Study Identification

OVID Embase and OVID MEDLINE databases were systematically searched from inception to March 23, 2021 using variations of the following search keywords: "psoriatic arthritis" AND specific biologics (see Supplemental File 1). In accordance with the predetermined inclusion criteria, titles/abstracts and full texts of retrieved articles were independently screened by two reviewers (A.A. and M.S.), and any conflicts were resolved by a third reviewer (A.M). A reviewer (A.A.) manually searched the reference lists of relevant reviews and studies to identify additional articles that may have been missed by the initial database search.

Inclusion Criteria

Original articles written in the English language were included if they:

1. reported intervention of interest (i.e., patients on biologic therapy),
2. involved study population (i.e., human participants that experienced an onset or exacerbation of PsA post-biologic initiation),
3. had an observational (i.e., case reports, case series, cross-sectional or cohort studies) study design.

Studies that included biologics as treatments for PsA or that did not provide specific individual patient data were excluded. Additionally, conference abstracts and studies with irretrievable full texts were excluded.

Data Extraction

Two reviewers (A.A and M.S.) independently extracted data on study characteristics (study author, study design, sample size), patient characteristics (age, sex, comorbidities, relevant family or personal history of conditions, concomitant medications, prior failed treatments), information on biologics (dose, frequency, mechanism), and characteristics of PsA diagnosis and progression (preexisting or de novo PsA, location, treatments, biologic discontinuations, resolution outcomes and recurrence or residual side-effects). The following terms were defined:

1. Latency period: duration between biologic initiation to PsA development or exacerbation.
2. Resolution: complete or partial resolution of PsA as reported by individual studies.
3. Resolution period: time from treatment initiation for PsA to partial or complete resolution of PsA.

Data Synthesis and Analysis

Due to the considerable heterogeneity of the included studies, meta-analysis was not performed. A descriptive analysis was conducted, and frequency data summated as percentages (%).

Quality and Adverse Drug Reaction Assessments

The quality of evidence was assessed by A.A. and M.S. using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[11] Additionally, causation probability between PsA development and offending drug was assessed using the Naranjo criteria.[12] For criteria 1, which evaluates the presence of previous conclusive reports on drug associated PsA reaction, "yes" was only scored if there were reports of the specific drug. For criteria 5, alternative causes that could on their own have caused PsA included the following conditions known to be associated with PsA: alopecia areata, pernicious anemia, psoriasis, Addison's disease, rheumatoid arthritis, adult-onset insulin dependent diabetes mellitus, cardiovascular disease, Lyme disease, Streptococcal infection, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and atopic disease.

Results

Screening of the initial titles and abstracts of 2065 studies was followed by full text screening of 103 articles, 18 articles fulfilled the preestablished inclusion criteria and were included in this systematic review (12 case reports, 4 case series, and 2 retrospective cohort studies and 1 prospective cohort study) (Supplemental File 2).[13-29] Overall, 64 patients reported PsA-related complications while on biologics (Supplementary File 3). These patients had a mean age of 50.8 years, ranging from 17 to 85 years. Of the 64 patients that reported sex, males comprised of 53.1% (n = 34/64) and females of 46.9% (n = 30/64) (Supplemental File 4). The

collected patient demographics are in line with PsA development in the general populace[6]

Of the 64 patients, 89.1% (n = 57/64) experienced PsA onset and 10.9% (n = 7/64) experienced exacerbation of pre-existing PsA after administration of the following reported biologics: TNF-α inhibitors (42.2%, n = 27/64), IL-12/23 inhibitor (39.1%, n = 25/64), IL-17 inhibitor (10.9%, n = 7/64), CD-20 inhibitor (4.7%, n = 3/64), IL-23 inhibitor (1.6%, n = 1/64), and α4-integrin monoclonal antibody (1.6%, n = 1/64) (Supplemental File 5). These biologics were given predominantly for indications such as psoriasis (89.1%, n = 57/64), rheumatoid arthritis (6.3%, n = 4/64), and Crohn's disease (1.6%, n = 1/64). Common locations of joints affected included the hands (n = 17), feet (n = 8), and knees (n = 7). Mean duration of psoriasis in patients was 17.2 years (n = 32/64).

The mean duration of exposure to biologics before PsA development or exacerbation was 14.8 months (range: 1 to 48) and 5.2 months (range: 0.25 to 12), respectively. The mean duration ranged from 14.9 months for ustekinumab (IL-12/23 inhibitor) to 1 week for brodalumab (IL-17 inhibitor). Biologics were maintained with Ustekinumab in 5.6% (n = 3/54) and Rituximab in 1.9% (n = 1/54) of cases and withdrawn in 51.9% (n = 28/54) after appearance of PsA related complications; withdrawal information was not available for 40.7% (n = 22/54) of cases.

A specific treatment for PsA was reported for 64 patients, including discontinuation of biologics (32.8%, n = 21/64) and/or treatment with corticosteroids (10.9%, n = 7/64) and ustekinumab (10.9%, n = 7/64), respectively. Complete resolution of PsA was observed in 35.9% (n = 23/64) of cases; 56.2% (n = 13/23) after biologic discontinuations only (mean resolution period of 6.3 months), 30.4% (n = 7/23) of cases after biologic discontinuation and treatment (mean resolution period of 1.7 months), and 8.7% (n = 2/23) after biologic continuation and treatment (mean resolution period not reported). Whereas, partial resolution was achieved in 3.1% (n = 2/64) of cases after biologic discontinuation and treatment (n = 1), and biologic discontinuation only (n = 1); mean resolution period was not reported. Additionally, 24 patients switched to an alternate biologic for the primary indication including: adalimumab (n = 7), ustekinumab (n = 5), secukinumab (n = 4), etanercept (n = 3), infliximab (n = 2), guselkumab, rituximab, and golimumab (n = 1 each) (Supplemental File 5); no PsA related adverse events were reported after the switch to another biologic agent.

Discussion

Various paradoxical reactions in patients using biologics have been described in the literature. This systematic review summarized the characteristics and outcomes of PsA-related complications in patients on biologic therapy. The results show that a total of 64 patients, majority being treated for psoriasis (89.1%), experienced new onset or worsening of PsA during biologic therapy. Among these, 42.2% were receiving TNF-α inhibitors, 39.1% were on IL-12/23 inhibitors, 10.9% on IL-17A inhibitors, 4.7% on CD-20 inhibitors, and 1.6% on α4-integrin monoclonal antibodies and IL-23 Inhibitors each . The mean duration between biologic initiation and PsA onset or exacerbation was 14.8 months and 5.2 months respectively. Some cases were successfully treated with discontinuation of the biologic alone (32.8%), while others required further treatment with corticosteroids or ustekinumab.

We found TNF-α and IL-12/23 inhibitors were the most common biologics associated with PsA development or worsening. Various hypotheses have been proposed to mechanistically explain this paradoxical adverse reaction. First, biologic agents lead to an imbalance in cytokine levels, resulting in psoriatic joint inflammation.[30,31] Patients with PsA have increased levels of IL-12 and IL-23.[32] Furthermore, IL-23 is responsible for stimulating the production of Th17 cells that are capable of acting as osteoclastogenic T cells, which may result in erosive joint disease.[18] Second, some biologics may be less efficacious in the joints compared to the skin, resulting in subclinical arthritis, which manifests as joint inflammation without skin lesions.[31] Lastly, antinuclear antibodies (ANA) have reportedly been elevated by anti-TNF antibodies.[33] Literature shows that 14% to 16% of patients being treated with adalimumab have a rise or conversion in ANA titres, which are associated with various autoimmune diseases such as PsA.[34,35] Similarly, a study by Pirowska et al. reported that elevated ANA in patients with PsA was induced by all anti-TNF treatments including infliximab, etanercept, and adalimumab.[36] By inhibiting the effects of TNF, anti-TNF antibodies induce the production of interferon (IFN) from plasmacytoid dendritic cells.[37] IFN induction was shown to raise ANA levels and may, therefore, contribute to the paradoxical PsA.[29,37]

Our systematic review found that improvements in PsA occurred after switching to ustekinumab and adalimumab in 20.8% and 29.2% of patients, respectively. Previous clinical trials reported greater efficacy for treatment of PsA with these agents. For example, treatment with 90 mg of ustekinumab every 4 weeks achieved an ACR20 (20% improvement based on criteria from the American College of Rheumatology) response at 24 weeks in 42% of patients compared to only 14% in the placebo group, with an absolute difference of 28% (CI 14.0–41.6, $P < .001$).[38] Other trials focusing on adalimumab reported similar outcomes.[39,40] A double-blind study comparing adalimumab to placebo in patients with PsA reported improvements in skin and joint manifestations following biologic therapy.[40] At 48 weeks, patients treated with adalimumab achieved ACR20, ACR50, and ACR70 responses at rates of 56%, 44%, and 30%, respectively.[40] The differences between efficacy observed in our study compared to previous trials may be

linked to heterogenous data, variable time of follow up and harder to treat patients with refractory inflammatory conditions.

In addition to being a paradoxical adverse effect of biologic treatment, PsA development or exacerbation is a common complication in patients with psoriasis suggesting an increased risk to develop this condition in our patient cohort even prior to biologic treatment.[41] For instance, Alinaghi et al. reported the incidence of PsA to be 19.7% in patients with psoriasis and 25% for those with moderate to severe psoriasis.[41] In our systematic review, 87.0% of patients presented with psoriasis prior to PsA development or exacerbation. Furthermore, a study by Carubbi et al. reported an association between PsA and other inflammatory diseases including Crohn's disease, ulcerative colitis, and rheumatoid arthritis.[42] Similarly, our study included patients with Crohn's disease and rheumatoid arthritis. As a result, it is important to note that patients may have experienced new onset or worsening of PsA as a manifestation of underlying diseases, with the onset or exacerbation secondary to biologic use being coincidental.

There are several important limitations in this systematic review. All summarized cases were observational with small sample sizes and heterogenous data, thereby limiting the collected data and generalizability of findings. Since the mean Naranjo score was low (4.63), it may be difficult to conclude causality between biologic use and PsA onset or exacerbation. Second, we were not able to obtain additional information regarding family history and comorbidities from the included studies. There were no re-challenge tests performed and therefore it is unclear whether the biologic was associated with PsA related adverse effects. Additionally, most patients included in this review had underlying conditions that may have increased their risk of developing PsA; it is therefore, possible that insufficient control of the preexisting condition indicated for biologic use led to PsA related complications. Alternatively, PsA onset could be idiopathic and independent from the preexisting condition or the biologic use. It is also important to note that the treatments highlighted in this manuscript are effective treatments for PsA, but it is possible that breakthrough cases of PsA may be included in the patient sample due to treatment failures. Ultimately, further studies and large clinical trials are warranted to elucidate the causality, pathophysiology and management strategies for patients that develop or experience exacerbation of PsA while being treated with biologic therapies.

Despite these limitations, our systematic review suggests that TNF-α and IL-12/23 inhibitors are the most common biologics associated with PsA. Given the significant impact of PsA on the quality of life and function of the patients,[43] surveillance for PsA related complications in patients on biologic therapy are important for timely diagnosis and optimal resolution outcomes. Collaborative care between the dermatologist and rheumatologist should be emphasized in diagnosing and managing patients who show any indication of joint inflammation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Jensen Yeung has been a speaker, consultant, and investigator for AbbVie, Allergan, Amgen, Astellas, Boehringer Ingelheim, Celgene, Centocor, Coherus, Dermira, Eli Lilly, Forward, Galderma, GSK, Janssen, Leo, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, Valeant, and Xenon. Other authors do not have any conflicts of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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