Rheumatology Advances in Practice, 2023, **7(2)**, rkad049
https://doi.org/10.1093/rap/rkad049
Advance access publication 9 June 2023
Concise Report

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Clinical science

Tofacitinib as monotherapy in cutaneous polyarteritis nodosa: a case series

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Abstract

Objective: Cutaneous polyarteritis nodosa (CPAN) is a distinct clinical entity represented by a chronic, relapsing, benign course, with rare systemic involvement. Treatment is with CSs, CYC or other conventional synthetic DMARDs (csDMARDs). In this case series, we aimed to share our varied clinical experience of successfully treating patients with CPAN, with tofacitinib in a refractory/relapsing course or as upfront monotherapy without CSs/csDMARDs.

Methods: We report this retrospective case series managed at our rheumatology centre in Bangalore from 2019 to 2022. Four patients identified as CPAN on biopsy were able to achieve disease-free remission with tofacitinib as part of their treatment, with no relapse on further follow-up. Our patients presented with subcutaneous nodules and cutaneous ulcers. After systemic evaluation, all the patients underwent skin biopsy, which showed fibrinoid necrosis in the vessel walls of the dermis, with a histopathological impression of CPAN. They were initially treated with a conventional approach of CSs with/without csDMARDs. On experiencing a refractory/relapsing course, tofacitinib was tried in all the patients as either CS sparing or upfront monotherapy without concomitant csDMARDs.

Results: Use of tofacitinib resulted in improvement of ulcers and paraesthesia and in gradual healing of skin lesions, albeit with scarring, with no further recurrence or relapse over a follow-up period of 6 months for all the patients. The therapeutic effect of tofacitinib was consistent when used either as CS sparing or as upfront monotherapy, thereby proving the drug to be a promising option that warrants larger trials in future to treat the subset of patients with established CPAN.

Conclusion: Tofacitinib could be used for disease-free remission as monotherapy for CPAN either upfront or as CS sparing, even without concomitant csDMARDs, in those patients who are dependent on CSs or multiple DMARDs.

Lay Summary

What does this mean for patients?

Cutaneous polyarteritis nodosa (CPAN) is a rare disease that causes frequently recurring and often chronic skin lesions. Corticosteroids (CSs) and other drugs are used to treat it, but some patients may not respond well or may have side effects. In this case series, it was found that tofacitinib, a medication used to treat people with rheumatoid arthritis, was effective in treating CPAN in four patients. When we followed up the patients, they had achieved disease-free remission with no relapse. Some patients were able to stop taking CSs and other drugs after starting tofacitinib. It is suggested that tofacitinib could be used as a monotherapy (i.e. without combining it with other drugs) for CPAN to reduce the need for CSs and other drugs. It is hoped that future researchers will find these data encouraging and might conduct larger trials to investigate the use of tofacitnib to treat CPAN.

Keywords: cutaneous polyarteritis nodosa, livedo reticularis, subcutaneous nodules, leucocytoclastic vasculitis, fibrinoid necrosis, tofacitinib, Janus kinase inhibitors

Key messages

- Patients with cutaneous PAN often remain CS dependent or may warrant use of multiple DMARDs for disease control.
- Tofacitinib, when used as monotherapy, is an option for achieving remission in cutaneous PAN.
- Tofacitinib showed good results either as upfront therapy or as CS sparing and warrants larger trials in these clinical settings.

Introduction

Cutaneous polyarteritis nodosa (CPAN) is a rare form of cutaneous vasculitis involving small and medium-sized arteries of the dermis and subcutaneous tissue [1]. The aetiopathogenesis is mostly unclear [2]. The characteristic manifestations are tender subcutaneous nodules, livedo reticularis and subcutaneous ulcerations [1]. The diagnosis is predominantly on clinical and histological findings [3].

Received: 27 March 2023. **Accepted:** 10 May 2023

The clinical course of CPAN is usually not life-threatening but can be disfiguring, indolent and painful to these patients, affecting their activities and sleep, hence affecting their quality of life.

Ethics

This study was approved by the ACE Independent Ethics Committee, Bangalore (DCGI reg. no. ECR/141/Indt/KA/2013/RR-19; NABH certificate number EC-CT-2018-0029). The ACE Independent Ethics Committee functions in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Guideline for Good Clinical Practice (GCP) Guideline, Ethical Guideline for Biomedical research in human subjects by Indian Council of Medical Research (ICMR), New Delhi and according to the requirements laid down in the Indian GCP and in accordance with the new Drugs and Clinical Trial rules 2019. Written informed consent was obtained from all the patients/participants.

Case series

Case 1

A 32-year-old female presented initially with a history of paraesthesia in glove-and-stocking distribution and pruritic racemose rashes all over the body of 2 months duration. These were intermittent and self-limiting, hence no clinical intervention was sought. However, she complained of multiple subcutaneous ulcers predominantly distributed over both lower limbs for the last 2 weeks. Our investigations ruled out any systemic involvement and demonstrated elevated inflammatory markers (Tables 1 and 2). A skin biopsy taken from the subcutaneous nodule on the ankle revealed deposition of fibrinoid material in the vessel wall and vessel lumen of the dermis.

She was initially diagnosed with cutaneous vasculitis (small vessel vasculitis) elsewhere and treated with oral MTX 15 mg/week, prednisolone 20 mg/day and colchicine 0.5 mg/day, which was stopped abruptly by the patient after remission, owing to weight gain.

She later presented to us with a history of sudden onset of persistent pruritus on the foot, arms, thighs and back, which eventually increased in intensity and frequency. She also gave a history of paraesthesia and bluish discoloration of the skin on her legs and hands, which worsened on exposure to cold temperatures, consistent with livedo reticularis (Fig. 1A). She received an initial course of oral tofacitinib 5 mg twice a day (monotherapy, without CSs or MTX), pregabalin 50 mg/day and fexofenadine hydrochloride 120 mg/day for a month. CSs were avoided because the patient already had a high BMI. MTX was avoided because the patient developed gastrointestinal intolerance. The skin lesions and pruritus completely resolved over 1 month. She was later lost to follow-up and stopped the treatment herself owing to symptomatic improvement.

She presented to us again 5 months after the first visit with similar complaints, along with myalgia of the upper arm without any systemic involvement. Laboratory investigations showed a persistent rise in ESR, as mentioned in Table 1.

She was retreated with oral tofacitinib 5 mg twice a day, and etoricoxib 90 mg for pain when required for a month. Even after treatment withdrawal and flare, she responded within 12 weeks to tofacitinib monotherapy without CSs or

Table 1. Clinical summary and follow-up

Parameter	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	32	28	65	32
Sex	Female	Female	Male	Female
Clinical presentation	Paraesthesia in glove-and-stocking distribution, pruritic livedo reticularis rashes, multiple subcutaneous nodules, bluish discoloration of skin on both hands and legs	Purpuric lesions on the bilateral lower extremities with pedal oedema	Left lateral malleolar non-healing superficial ulcer and paraesthesia in the left stocking area	Multiple pruritic purpuric rashes and non-healing ulcers on the foot
Histopathology	Deposition of fibrinoid material in the vessel wall and vessel lumen of the dermis	Leucocytoclastic vasculitis and fibrinoid necrosis of the small vessels in the upper and mid dermis	Fibrinoid necrosis in upper dermal vessels, with proliferating blood vessels lined by plump endothelial cells	Fibrinoid necrosis of the vessel wall involving medium-sized vessels and necrotizing leucocytoclastic vasculitis of medium-sized blood vessels
Course of treatment	Initially on oral MTX 15 mg/week, prednisolone 20 mg/day and colchicine 0.5 mg/day Relapse after stopping CSs and conventional synthetic DMARDs Was then started on tofacitinib monotherapy 5 mg twice daily	Initially on prednisolone 25 mg/day, AZA 100 mg/day, and CSA 100 mg/day Relapse while on CSs, AZA and CSA Was then started on tofacitinib monotherapy 5 mg twice daily	Tofacitinib monotherapy, 5 mg twice daily, without CSs or conventional synthetic DMARDs	Tofacitinib monotherapy, 5 mg twice daily, without CSs or conventional synthetic DMARDs
Follow-up (24 weeks/6 months)	Patient is in persistent remission, with no relapse post tofacitinib therapy, with significantly decreased paraesthesia and healing of ulcers	Patient is in persistent remission, with no relapse post tofacitinib therapy, with significantly decreased paraesthesia and healing of ulcers	Patient is in persistent remission, with no relapse post tofacitinib therapy, with significantly decreased paraesthesia and healing of ulcers	Patient is in persistent remission. with no relapse post tofacitinib therapy, with significantly decreased paraesthesia and healing of ulcers

Table 2. Baseline investigations

Patient	Patient 1	Patient 2	Patient 3	Patient 4
Haemoglobin, g/dl	14.2	13.9	13.6	11.8
Total leucocyte count, /mm^3	10 750	8950	9100	9900
Platelets, lacs	3.5	2.7	2.9	4.1
Liver Function test	Within normal limits	Within normal limits	Within normal limits	Within normal limits
ESR, mm/h	57	15	12	34
CRP, mg/l, mean (range)	8.5 (0–5)	8.76 (0–5)	17 (0–5)	34.24 (0–5)
cANCA/pANCA/ANA/ RF/APLA	Negative	Negative	Negative	Negative
C3/C4	Normal	Normal	Normal	Normal
Creatinine, mg/dl	0.66	0.7	0.86	0.98
Viral markers (HBsAg/anti-HCV/HIV)	Negative	Negative	Negative	Negative
Urine routine and microscopy	Within normal limits	Within normal limits	Within normal limits	Within normal limits
Chest X-ray	Normal study	Normal study	Normal study	Normal study
Ultrasonography (USG) whole abdomen	Normal study	Normal study	Normal study	Normal study
ECG/cchocardiography	Normal study	Normal study	Normal study	Normal study
EMG and nerve conduction velocity	Normal study	Normal study	Normal study	Normal study

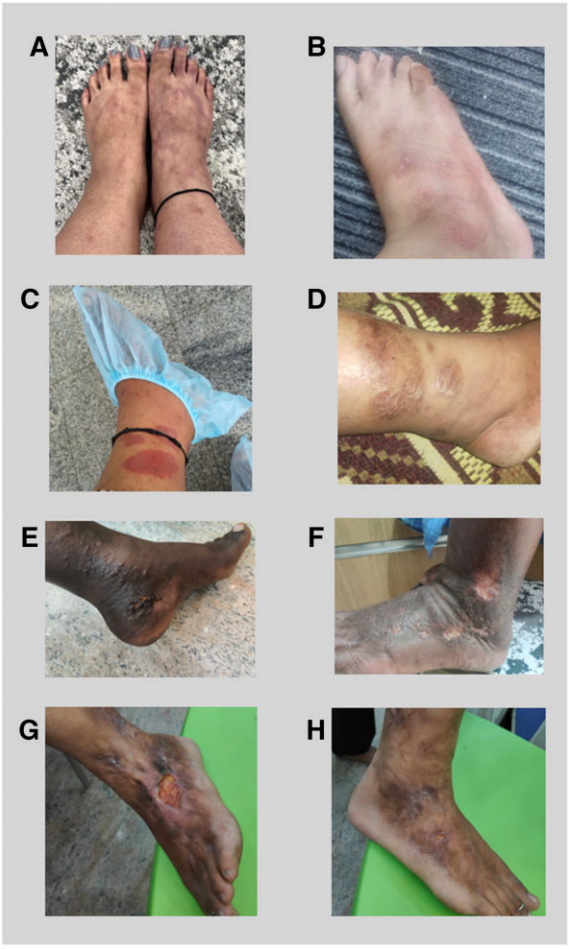

Figure 1. Comparison of cutaneous PAN ulcers/skin lesions before and after treatment with tofacitinib. (**A**, **B**) Patient 1: Livedo racemosa on both lower limbs (pre-ulcerative stage; A) and healed cutaneous lesion after 12 weeks of tofacitinib treatment (B). (**C**, **D**) Patient 2: purpuric lesions on bilateral lower extremities, with pedal oedema (C) and rapid regression of ulcers with scarring after tofacitinib therapy (D). (**E**, **F**) Patient 3: left lateral malleolar non-healing superficial ulcer (E) and healed cutaneous ulcers after tofacitinib therapy (F). (**G**, **H**) Patient 4: multiple non-healing ulcers on the foot (G) and ulcers healed with fibrosis after tofacitinib therapy (H)

MTX (Fig. 1B) and is in follow-up (6 months/24 weeks) without relapse. This suggests that tofacitinib monotherapy resulted in consistent and repetitive response to treatment in this patient.

Case 2

A 28-year-old female patient presented to us with purpuric lesions on her bilateral lower extremities, with pedal oedema (Fig. 1C). There was no history of any fever/joint involvement and no systemic involvement on evaluation (Tables 1 and 2). On performing a skin biopsy, the right leg revealed leucocytoclastic vasculitis (Fig. 2A) and fibrinoid necrosis of the small vessels in the upper and mid dermis, which, on histopathological review, was consistent with CPAN. Initially, she was started on a combination of prednisolone and AZA. However, we noticed a flare-up of rashes with doses of prednisolone <10 mg/day even after optimizing the dose of AZA. CSA was combined with AZA for a CS-sparing action. Nonetheless, further flare-up was noticed despite adding these two drugs, ultimately making the patient CS dependent. Hence, AZA and CSA were withdrawn and tofacitinib was started with a view to stopping CSs. There was subsequently an improvement in inflammatory markers and a rapid regression of ulcers with scarring, even after completely stopping CSs as, shown in Fig. 1D. The patient is in follow-up (6 months/24 weeks), without relapse.

Case 3

A 65-year-old male patient presented with a 1-month history of left lateral malleolar non-healing superficial ulcer and paraesthesia in the left stocking area (Fig. 1E). His vital signs were within normal limits. Our evaluation ruled out any systemic involvement, with an elevation of inflammatory markers (Tables 1 and 2). Ulcer biopsy revealed fibrinoid necrosis in upper dermal vessels, with proliferating blood vessels lined by plump endothelial cells (Fig. 2B). Ulcer biopsy was consistent with CPAN according to histopathological review. Primary treatment was with oral tofacitinib 5 mg twice a day, knowing its efficacy in the previous patient. There was a good and sustained response of ulcers to tofacitinib

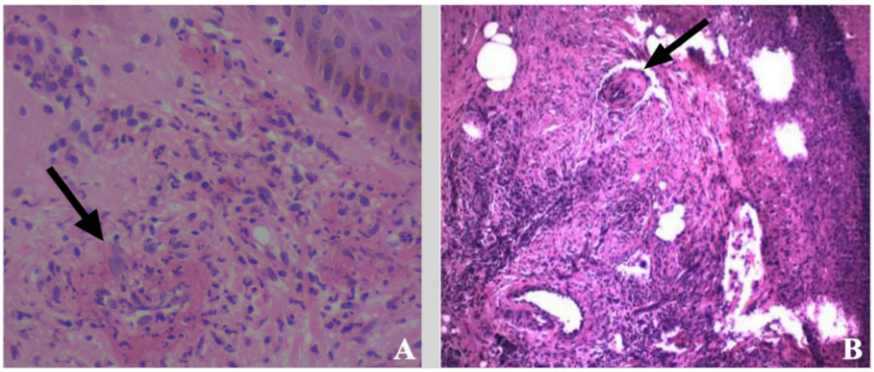

Figure 2. Skin biopsy findings of patients with cutaneous PAN. (**A**) Patient 2: small vessels in upper and mid dermis show fibrinoid necrosis and are surrounded and infiltrated by inflammatory cells, including neutrophils, lymphocytes, eosinophils with karyorrhectic debris. Leucocytoclastic vasculitis: skin biopsy from right leg. (**B**) Patient 3: the wall of the artery (arrow) shows a circumferential bright pink area of necrosis with protein deposition and inflammation (dark nuclei of neutrophil), i.e. fibrinoid necrosis. Patient 1 (not shown in figure): according to biopsy report, the dermis shows vessels with fibrinoid material deposition in the vessel wall and vessel lumen. The inflammatory infiltrate comprises a few lymphocytes and histiocytes. Features are suggestive of leucocytoclastic vasculitis. Patient 4 (not shown in figure): according to biopsy report, the epidermis shows papillomatosis, and hyperkeratosis with follicular plugging. The dermis shows perivascular lymphocytic infiltrate with fibrinoid necrosis of vessel wall involving medium-sized vessels, some of which are seen in the deepest dermis. Leucocytolysis is also seen. Biopsy skin from the leg shows necrotizing leucocytoclastic vasculitis involving medium-sized blood vessels

monotherapy without CSs or conventional synthetic DMARDs (csDMARDs) (Fig. 1F). The patient is in follow-up (6 months/24 weeks), without relapse.

Case 4

A 32-year-old female patient presented with multiple pruritic purpuric rashes and non-healing ulcers on the foot (Fig. 1G). Our evaluation ruled out any systemic involvement, with an elevation of inflammatory markers (Tables 1 and 2). Fibrinoid necrosis of the vessel wall involving medium-sized vessels and necrotizing leucocytoclastic vasculitis of medium-sized blood vessels were confirmed by a skin biopsy from a leg ulcer, which was consistent with CPAN according to histopathological review. The patient was started on tofacitinib monotherapy without CSs or csDMARDs based on the previous responses of patients with CPAN. The ulcers healed with fibrosis and scarring [Fig. 1H]. The patient is in follow-up (6 months/24 weeks), without relapse.

Discussion

In 1931, Lindberg first described CPAN [4]. The precise aetiology of CPAN remains unknown; however, the immune complex has some role to play in aetiopathogenesis [3]. In CPAN, lesions are restricted to the skin, adjacent muscles, nerves and joints [5]. Owing to their clinical nature, in the 2012 Revised International Chapel Hill Consensus CPAN was classified under single organ vasculitis as cutaneous arteritis [6]. CPAN manifests as tender subcutaneous nodules, livedo reticularis and ulceration, chiefly localized to the lower extremity [4]. Gangrene and necrosis of the fingers are very atypical findings [7]. A typical burst pattern of irregularly shaped livedo reticularis around an ulcer is highly suggestive of CPAN [8]. The subcutaneous tender, erythematous nodules (usually 0.5–3 cm in diameter) may either regress eventually or undergo ulceration [3]. Petechiae, purpura, cutaneous necrosis, auto-amputations and local extracutaneous manifestations such as arthralgia, myalgia, constitutional symptoms (such as fever and malaise) and peripheral neuropathy (mononeuropathy and mononeuritis multiplex) are other forms of clinical presentation [9].

The female predominance in CPAN has been reported in several studies, as in our case series. Rarely, it progresses to a systemic form [3]. In this concise report, no patient experienced disease-specific death or progression to the systemic form during the follow-up period [9]. Peripheral polyneuropathy was observed in two patients, which was localized to the CPAN-affected skin [9]. No patients presented with mononeuritis multiplex [9].

Although there are no specific clinical and laboratory findings [3], mild anaemia, moderate leucocytosis and an elevated ESR are laboratory abnormalities that are often encountered [10]. The ESR is elevated in $\leq$60% of CPAN patients [2]. A localized presentation, with systemic involvement being ruled out by evaluation, and concomitant histopathological findings confirmed the diagnosis in each patient [3]. The characteristic pathological feature is fibrinoid necrosis of the vessel wall and vessel lumen, with the presence of leucocytoclastic vasculitis in the small and medium-sized arteries [11].

Histopathological features of both CPAN and sytemic PAN are very similar, with features of necrotizing arteritis of small and medium-sized vessels [12]. Most severe cases are treated with CSs, which also remains the mainstay of treatment in CPAN [12]. CYC or other csDMARDs can be used in patients unresponsive to CS therapy [13]. However, long-term dependence on CSs has a plethora of adverse effects. CYC has several toxic effects, and sometimes patients respond inadequately to csDMARDs, hence the need for further therapeutic options.

Tofacitinib, which is an oral Janus kinase (JAK) 3/1 inhibitor, has been approved for the treatment of RA, PsA and AS in adults. It suppresses the inflammatory response by interfering with inflammatory cytokine signalling. However, its effectiveness in enhancing the armamentarium in treating CPAN/cutaneous arteritis is sparsely reported, such as by Zhu *et al.* [14] and Rimar *et al.* [15], who reported that patients have responded favourably to tofacitinib in refractory CPAN. Furthermore, to the best of our knowledge, there is no

published literature where tofacitinib monotherapy has been used initially to treat CPAN, with adequate response.

In our case series, the first two patients were treated initially with oral CSs and csDMARDs, which were eventually stopped, and tofacitinib was commenced as a monotherapy. Noticing a good response in patients 1 and 2, tofacitinib was used as the primary therapy in patients 3 and 4, achieving remission in all four patients. Table 1 provides a clinical summary of all the patients, and Table 2 elaborates the systemic evaluation done in each patient.

Our retrospective analysis indicates that the use of tofacitinib without CSs was not associated with relapse of cutaneous symptoms. Tofacitinib, however, has been known to be associated with secondary infections, such as herpes zoster, and should be used cautiously with patients at elevated cardiovascular risk. Hence, given that the long-term efficacy and safety of tofacitinib in CPAN are still unclear in its current approved indications, its use should be with cautious clinical supervision on a case-by-case basis until larger trials have been conducted.

Conclusion

In conclusion, our case series shows that tofacitinib could be considered as a prospective therapy in patients with CPAN. Given that tofacitinib use is limited to case series, further studies are needed to confirm this.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

All the authors took part in drafting the initial manuscript, and then critically reviewed and revised the manuscript. All authors then approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

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