Tocilizumab for the treatment of polyarteritis nodosa: a systematic literature review. Correspondence on 'Tofacitinib for polyarteritis nodosa: a tailored therapy' by Rimar *et al*

We read the paper by Rimar *et al*[1] in your journal with great interest. They reported the case with refractory polyarteritis nodosa treated with tofacitinib, a janus kinase inhibitor, successfully. As shown in their paper, recent advances in the era of biologic agents have improved the management of difficult-to-treat cases dramatically. Considering that tofacitinib blocks interleukin (IL)-6-mediated signalling pathway through inhibiting janus kinase 1, inhibiting IL-6 cascade may also be effective in polyarteritis nodosa. In this regard, tocilizumab, a biologic agent targeting IL-6 receptor, has shown its efficacy in a variety of diseases such as rheumatoid arthritis, adult-onset Still's disease, large-vessel vasculitis and Behcet's disease.[2–5] Although the precise pathogenesis of polyarteritis nodosa remains unclear, serum IL-6 levels correlate with disease severity, suggesting the involvement of IL-6 in the disease process.[6] Therefore, we assume that tocilizumab may benefit polyarteritis nodosa as a therapeutic option.

To investigate the effectiveness and safety profile of tocilizumab in patients with polyarteritis nodosa, we performed a systematic literature review from the inception dates until 23 July 2020. We used the PubMed database to identify all English publications using the Medical Subject Heading 'polyarteritis nodosa' and 'tocilizumab' and identified 13 potentially relevant articles. Among them, seven were excluded due to the following: four reviews, two duplicates and one non-related topic. Eventually, a total of 11 cases with polyarteritis nodosa treated with tocilizumab were identified from six articles (table 1).[7–12] The median age of the cases was 35 years old (range: 3–70), with equal sex distribution. The median disease duration at tocilizumab treatment was 38 months (range: 3–120). Clinical symptoms varied through the cases (online supplementary table 1). All patients showed high levels of serum C reactive protein (median, 19.7 mg/dL). As shown in table 1, the reasons for initiating tocilizumab were the following: nine cases with refractory to and/or relapsing clinical course by prior immunosuppressive treatments such as cyclophosphamide (n=6), methotrexate (n=4), mycophenolate mofetil (n=2), azathioprine (n=2), tacrolimus (n=1), anti-tumour necrosis factor agents (n=2), rituximab (n=1) and anakinra (n=1). In the other two cases, tocilizumab was initiated as a primary induction therapy. Tocilizumab was used as the intravenous administration at a dose of 8 mg/kg every 4 weeks in seven cases and every 2 weeks in one case, at a dose of 10 mg/kg every 4 weeks in one case and subcutaneous administration at a dose of 162 mg weekly in two cases. In seven cases, tocilizumab was used in combination with high-dose glucocorticoids (table 1). The median observation period after tocilizumab treatment was 12 months (range: 6–37). In all cases, tocilizumab rapidly improved clinical manifestations, mostly within a week, and glucocorticoids could be successfully tapered. All cases achieved asymptomatic condition at last visit. Glucocorticoids were completely stopped in three cases, while eight cases were receiving only low dose (≤5 mg/day) at last visit (table 1). No new safety signal or adverse event was reported.

As this literature review was based on case reports, in which positive results are inclined to be published, potential publication bias can exist. Further, the number of case reports was small due to the rarity of the disease. Nevertheless, tocilizumab is effective in cases of refractory/relapsing polyarteritis nodosa and showed its glucocorticoid-sparing effect. It could even achieve glucocorticoid-free in some cases. Generally, the prognosis of polyarteritis nodosa is poor, showing the 5-year survival rate as 13% if untreated and as 80% even if treated.[13] Our study along with the one by Rimar *et al* would shed light on the management of this rare disease by biologic agents to improve their prognosis. Future prospective randomised controlled trials are desired to confirm our results.

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Table 1 Characteristics and outcome of 11 patients with polyarteritis nodosa treated with tocilizumab

No	Age (years)	Sex	Disease duration (months)	Treatments before TCZ	CRP (mg/dL)	The reason for TCZ	Dose/frequency	Concomitant treatment	Observation (months)	PSL at last visit
1	11	F	43	GC, AZA, MMF, TAC, CyA, IvIg, ETN, IFX, ADA	Elevated	R	8 mg/kg IV every 2 weeks	PSL, MMF	7	Off
2	23	M	38	GC, CYC, MTX, RTX, ANA, IvIg	29.1	R	8 mg/kg IV every 4 weeks	PSL 80 mg/day	37	4 mg/day
3	24	M	NA	GC, CYC, IvIg	29.8	R	8 mg/kg IV every 4 weeks	mPSL 250 mg IV	11	5 mg/day
4	63	F	NA	GC	17.4	P	162 mg SC every week	PSL 50 mg/day	6	5 mg/day
5	70	F	NA	GC, MTX	9.3	R	8 mg/kg IV every 4 weeks	mPSL 500 mg IV	13	5 mg/day
6	67	M	6	GC, CYC	2.03	R	162 mg SC every week	PSL 16 mg/day, MTX	15	4 mg/day
7	39	F	120	GC, CYC, MTX, MMF, IFX	5.9–12.6	R	8 mg/kg IV every 4 weeks	PSL 50 mg/day	12	5 mg/day
8	52	F	96	GC, CYC, MTX, AZA, dapsone	Not mentioned	R	8 mg/kg IV every 4 weeks	PSL 35 mg/day	12	5 mg/day
9	35	M	3	GC, IvIg	39.3	R	8 mg/kg IV every 4 weeks	PSL 60 mg/day	10	Off
10	33	M	NA	GC, CYC	16.9	R	8 mg/kg IV every 4 weeks	PSL 4 mg/day	50	Off
11	3	M	9	None	21.9	P	10 mg/kg IV every 4 weeks	PSL 1 mg/kg/day, CYC	7	Tapered

ADA, adalimumab; ANA, anakinra; AZA, azathioprine; CRP, C reactive protein; CyA, cyclosporine A; CYC, cyclophosphamide; ETN, etanercept; GC, glucocorticoid; IFX, infliximab; IV , intravenous; IvIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not assessed; P, primary induction; PSL, prednisolone; R, refractory/relapsing; RTX, rituximab; SC, subcutaneous; TAC, tacrolimus; TCZ, tocilizumab.

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