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CASE BASED REVIEW

Tocilizumab treatment in refractory polyarteritis nodosa: a case report and review of the literature

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Abstract

Polyarteritis nodosa (PAN) is a rare systemic vasculitis affecting multiple organs. Current standard treatment includes the use of glucocorticoids and cyclophosphamide. Unfortunately, some patients do not respond to this treatment and other therapeutic options are needed. We present a case of a young male with refractory PAN and ongoing biopsy evidence of active vasculitis despite optimal standard therapies, who was successfully treated with interleukin-6 antagonist, tocilizumab. A 24-year-old male presented with severe immobilizing polyneuropathy and myalgias. Clinical features included fasciitis, tenosynovitis, early signs of polyneuropathy, and panniculitis, which were largely refractory to the standard therapies. The previous unsuccessful treatments included high-dose glucocorticoids, methotrexate, cyclophosphamide, rituximab, anakinra, and intravenous immunoglobulins. Magnetic resonance imaging showed signs of myositis, with muscle biopsy confirming the diagnosis of PAN. Rapid clinical improvement and sustained remission occurred after interleukin-6 inhibition with tocilizumab at increased dose of 800 mg every 4 weeks. The used search strategy identified 20 publications of which four articles were included for the further analysis. In total, we report the clinical outcome of five PAN cases from the literature and the present one. The present case and the systematic review of literature suggest that tocilizumab is a possible treatment option for, otherwise, refractory hepatitis B virus negative PAN. Randomized-controlled trials are required to evaluate the safety and efficacy of tocilizumab in PAN.

Keywords Polyarteritis nodosa · Tocilizumab · Biological therapy · Myositis · Vasculitis

Introduction

Polyarteritis nodosa (PAN) is a rare necrotizing systemic vasculitis of medium- and small-sized arteries that is not associated with antineutrophil cytoplasmic antibodies (ANCA) [1]. Although there are several different treatment approaches, clinical management can be difficult and prognosis is often poor.

The current standard treatment for hepatitis B virus negative (primary) PAN [2] includes the use of glucocorticoids for milder disease and a combination of glucocorticoids with cyclophosphamide for severe conditions. Unfortunately, some patients do not respond adequately to this treatment. Recent studies [3–5] support the use of biologic therapies, such as rituximab, infliximab, and other tumor necrosis factor (TNF) antagonists as a possible option in recalcitrant cases. However, the use of biologics in PAN has not been investigated in randomized clinical trials yet.

Interleukin-6 mediates various proinflammatory processes and is involved in the pathogenesis of systemic inflammatory diseases [6, 7]. Moreover, the previous studies showed that circulating interleukin-6 levels in (cutaneous) PAN correlate with disease activity [8–10]. Interleukin-6 signalling could, therefore, be a promising target in the clinical management of PAN [11]. Tocilizumab, a humanized monoclonal anti-interleukin-6 receptor antibody, has been

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successfully used for the treatment of ANCA-negative vasculitis [4], including giant-cell arteritis [12] and Takayasu arteritis [13]. To our knowledge, there are only a few case reports [14–17] describing the clinical effects of tocilizumab in PAN. Nevertheless, these studies suggest beneficial effects of tocilizumab in PAN. Supporting these results, we present a case of a young male with epimysial vasculitis of the lower leg in therapy-resistant PAN who was successfully treated with tocilizumab.

Since the clinical effects of tocilizumab in PAN have not been investigated systematically, we performed a systematic review on this issue. Thus, the aims of the present study were (1) to report our own experience with tocilizumab in refractory PAN and (2) to systematically identify and analyse the studies of PAN patients who have been treated with tocilizumab to evaluate this treatment option.

Methods

Literature search

A systematic literature search with no restriction to publication date was conducted on 01/08/2018. We searched the database PubMed for English studies that investigated the role of tocilizumab in PAN using the combined terms "polyarteritis nodosa", "periarteritis nodosa", "tocilizumab", "actemra", "interleukin-6 antagonist", "IL-6 antagonist", "interleukin-6", "IL-6", "anti-interleukin-6", "anti-IL-6", "interleukin-6 blockade", "IL-6 blockade", "biologic therapy", and "biological therapy" for Title/Abstract. All articles were independently reviewed in full text by two reviewers (MK and NR). In addition, reference lists of the reviewed articles were screened for further inclusions.

Study selection

Primary studies providing empirical data regarding the effects of tocilizumab in PAN were included. The following inclusion criteria were applied: (1) article published in English language; (2) tocilizumab was used for the treatment of PAN; (3) tocilizumab regimen was reported; (4) clinical course and outcome of the patient were reported; (5) original paper was published in a peer-reviewed journal. Reviews and other study types lacking clinical data from individual patients were excluded. Throughout the selection process, there was no disagreement between the two reviewers.

Data extraction

Individual patient data described within the included articles were analysed and extracted: clinical, laboratory, imaging, and histological data; previous treatment; tocilizumab regime; outcome; follow-up. The extracted data were summarized (Table 1).

Case presentation

In February 2013, a 21-year-old male was admitted with fever as accompanied by generalised muscle pain and weakness of the upper and lower limbs. The patient also reported a significant weight loss of 14 kg in the previous weeks (67 kg body weight at presentation). Increased C-reactive protein (CRP) (> 300 mg/L; normal < 5 mg/L) was noted, but autoimmune and infectious serology (including human immunodeficiency virus and hepatitis) were negative. Magnetic resonance imaging (MRI) indicated features suggestive of fasciitis of the forearm, as well as joint effusion and tenosynovitis of the wrist. Treatment with steroids was initiated (100 mg prednisolone daily for 3 days, reduced to prednisolone 60 mg for 7 days, tapered by 10 mg per week) and the patient was transferred to a rheumatology centre.

A positron emission tomography scan showed inhomogeneous metabolic activity of the muscles, especially of the upper limbs, suspicious for myositis. Due to a livedo racemosa of the arms and legs, a skin biopsy was also performed which revealed panniculitis with vasculitis of the small- and medium-sized vessels.

The patient was then transferred to a tertiary centre for rare diseases. The working differential diagnosis at that stage included atypical rheumatoid arthritis, Still's disease, and undifferentiated autoinflammatory syndrome. Therefore, he was started on treatment with methotrexate 20 mg subcutaneously (sc) and anakinra 100 mg sc. As he was also found to have immunoglobulin A and mild immunoglobulin M deficiency were diagnosed and intravenous immunoglobulin treatment (5 × 20 g) was initiated. The fever and myalgia improved, but the CRP remained elevated (initially 291 mg/L, after treatment with anakinra 18.2 mg/L), and it was not possible to reduce the glucocorticoids below a dose of 40 mg prednisolone daily without recurrence of arthralgia symptoms.

Therefore, anakinra was discontinued after 3 weeks and treatment with 400 mg tocilizumab intravenous (iv) every 2 weeks was initiated. The patient's condition improved and CRP normalized (3 mg/L) rapidly within days after the first iv infusion.

The patient sought advice for a second opinion in another rheumatology centre where the preferred diagnosis was undifferentiated small-/medium-sized vessel vasculitis. Tocilizumab and methotrexate were stopped after 3 months of treatment and monthly treatment of 1200 mg cyclophosphamide iv was initiated in July 2013. The patient received a total of nine infusions with a cumulative dose of 10.8 g of cyclophosphamide.

Table 1 Clinical manifestations and outcome of our case and polyarteritis nodosa cases retrieved from the literature treated with tocilizumab

References	Age (years)	Gender	ACR criteria	Symptoms	Laboratory			Imaging	Biopsy/histology	Treatment		Outcome
					ANCA	CRP	HBV			Previous treatment	TCZ regime	
Case 1 Our case PAN	23	Male	+	Livedo racemosa Striae distensae Myalgias Sensorimotor polyneuropathy Subcutaneous ulcerating nodules	–	Initial: 291 m/L After TCZ 1 mg/L	–	Initial MRI: no pathological finding Second MRI: severe myositis of both lower legs	Initial skin and muscle biopsy: unspecific findings Second muscle biopsy: necrotizing vasculitis of the epimysial arteries	GC MTX RTX CYC ANR IVIG	Initially TCZ 8 mg/kg every 4 weeks + IVIG + prednisolone 80 mg/day Later increased TCZ 10 mg/kg every 4 weeks	Asymptomatic with sustained remission GC tapering: prednisolone 5 mg/day still required Follow-up: 2 years
Case 2 [17] (Case 1) PAN	39	Female	+	Necrotic purpura Constitutional symptoms Myalgias Weight loss	–	Initial: 59–126 mg/L After TCZ 1 mg/L	–	Renal artery imaging: aneurysm	Deep skin biopsy: small and medium-vessel vasculitis	MTX MMF + GC CYC INF + GC + MTX CYC + GC	TCZ 8 mg/kg every 4 weeks+ prednisolone 50 mg/day	Asymptomatic with sustained remission GC tapering prednisolone 5 mg/day still required Follow-up: 1 year
Case 3 [17] (Case 2) PAN	52	Female	+	Skin: necrotic purpura livedo reticularis bubbles intraoral ulcerations arthritis myalgias polyneuropathy weight loss	*	*	–	MR angiography right arm: multiple aneurysms	Deep skin biopsy: small and medium-vessel vasculitis	COL + GC + DAP MTX + GC CYC + GC AZA	TCZ 8 mg/kg every 4 weeks + prednisolone 35 mg/day	Asymptomatic with sustained remission GC tapering prednisolone 5 mg/day still required Follow-up: 1 year
Case 4 [17] (Case 3) PAN	35	Male	+	Multiple arthritis Myalgia Tenosynovitis Subcutaneous nodules Paresthesia Weight loss	–	Initial 393 mg/L After TCZ 12 mg/L	–	FDG-PET/CT: FDG uptake in the bone marrow, subcutaneous nodules, intramuscular nodules	Deep skin biopsy: necrosis inflammation of small-sized and medium-sized vessels	GC GC + IVIG	TCZ 8 mg/kg every 4 weeks + prednisolone 70 mg/day Later: TCZ 8 mg/kg every 6 weeks	Normal FDG-PET/CT after 4 months GC tapering: no GC required Follow-up: 10 months

Table 1 (continued)

References	Age (years)	Gender	ACR criteria	Symptoms	Laboratory			Imaging	Biopsy/histology	Treatment		Outcome
					ANCA	CRP	HBV			Previous treatment	TCZ regime	
Case 5 [15] PAN	3	Male	+	Recurrent fever Periostitis Epididymoorchitis Arthritis Myositis	*	Initial: 200–300 mg/L	–	CT Angiography: bilateral vertebral artery vasculitis	No skin or muscle biopsy performed Bone marrow biopsy: normal	IVIG + low dose aspirin GC + INF	TCZ 10 mg/kg monthly + CYC 500 mg/m^2 + prednisolone 1 mg/kg/day	Clinical serological and imaging improvement GC tapering: * Follow-up: 6 months
Case 6 [14, 16] PAN with AA amyloidosis	33	Male	+	Crural skin ulcers Multiple intestine perforations Arterial hypertension Myalgias Weight loss Testicular pain Adhesive ileus Nodular skin changes	–	Initial: 169 mg/L After TCZ: 1 mg/L (hs-CRP)	–	Echocardiography: left ventricular concentric hypertrophy Echocardiography: dilated left ventricle, left ventricular hypertrophy, lowered ejection fraction	Small intestine segment: necrotizing vasculitis of the small- and medium-sized arteries Bioptic material from laparotomy: AA amyloidosis Kidney biopsy: deposits of amyloid in the glomeruli and vascular walls	GC + CYC	TCZ 8 mg/kg every 4 weeks + prednisolone 4 mg/day	Improvement of the renal and vascular deposits Stable cardiac function GC tapering: no GC required Follow-up: 50 months

ACR American College of Rheumatology, *ANR* anakinra, *AZA* azathioprine, *COL* colchicine, *CYC* cyclophosphamide, *DAP* dapsone, *FDG-PET* fluorodeoxyglucose positron emission tomography, *GC* glucocorticoids, *HBV* hepatitis B virus, *INF* infliximab, *IVIG* intravenous immunoglobulin, *MMF* mycophenolate mofetil, *MTX* methotrexate, *RTX* rituximab, *TCZ* tocilizumab, * was not specifically mentioned in the article

In February 2014, the patient was still dependent on 20 mg prednisolone daily with elevated inflammatory markers (CRP 82 mg/L) and synovitis of the wrists. Therefore, treatment was changed to rituximab (900 mg weekly for 4 weeks). 3 months after the last rituximab infusion, the patient's condition declined further to the extent that he was mobile only with the aid of crutches. CRP levels remained elevated (63 mg/L); therefore, treatment with tocilizumab 400 mg iv and intravenous immunoglobulin 20 g (every 4 weeks) was started again and the patient's condition improved. CRP levels initially decreased after the infusions (14.1 mg/L) but increased within the next month (200 mg/L), so that tocilizumab dosage was raised up to 800 mg iv every 4 weeks and CRP finally normalized (0.2 mg/L).

On the first evaluation in our hospital in August 2014, the patient was clinically stable on this therapeutic regime. Apart from striae distensae and livedo racemosa of the lower arms and legs (Fig. 1), clinical examination was normal (body weight 80 kg). Blood test results, in particular inflammatory markers, showed no abnormalities.

Taking the patient's medical history and the livedo racemosa into account, we suspected PAN to be responsible for the reported conditions. As the further course of disease was stable, intravenous immunoglobulin was discontinued and tocilizumab was reduced to 680 mg every 4 weeks in January 2016.

In March 2016, he was readmitted to the emergency room of our hospital. He reported achillodynia and acute pain of the calves and unintended weight loss of 4 kg. Clinical examination revealed no pathological findings, specifically normal perfusion. Musculoskeletal ultrasound showed no signs of tenosynovitis or arthritis. Blood tests were normal, including creatine kinase and CRP (2.1 mg/L). The myalgias were treated with prednisolone therapy (60 mg/day, tapered by 10 mg per week to 30 mg/day, tapered by 5 mg per week to 20 mg/day, tapered by 2.5 mg every 2 weeks). However, he had worsening myalgias and electroneurography showed the early signs of sensorimotor neuropathy of both legs.

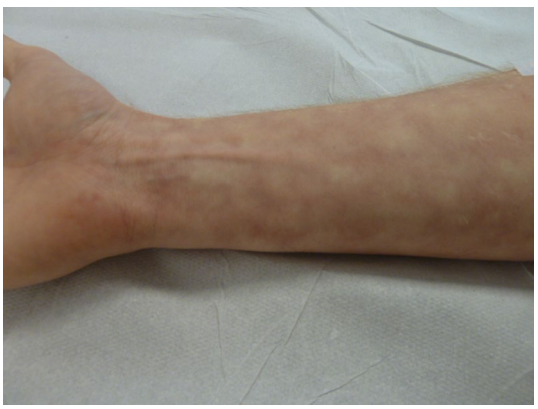

Fig. 1 Livedo racemosa of the upper limb in polyarteritis nodosa

At the request of the patient, we, therefore, added intravenous immunoglobulin to the regimen. Despite therapy with high-dose glucocorticoids, intravenous immunoglobulin, and tocilizumab 680 mg iv, the myalgias worsened further, resulting in severely reduced mobility. In addition, small subcutaneous, partly ulcerating nodules appeared at the patient's lower legs and face (Fig. 2).

An MRI demonstrated signs of severe myositis of both lower legs (Fig. 3a). Biopsy of the gastrocnemius muscle revealed a necrotizing vasculitis of the epimysial arteries and arterioles with ischemic damages of the muscle tissue [18] (Fig. 4), confirming that the suspected diagnosis of

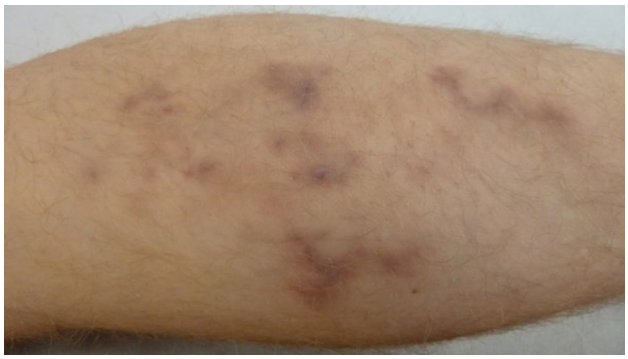

Fig. 2 Subcutaneous partly ulcerating nodules of the lower legs in a patient with polyarteritis nodosa

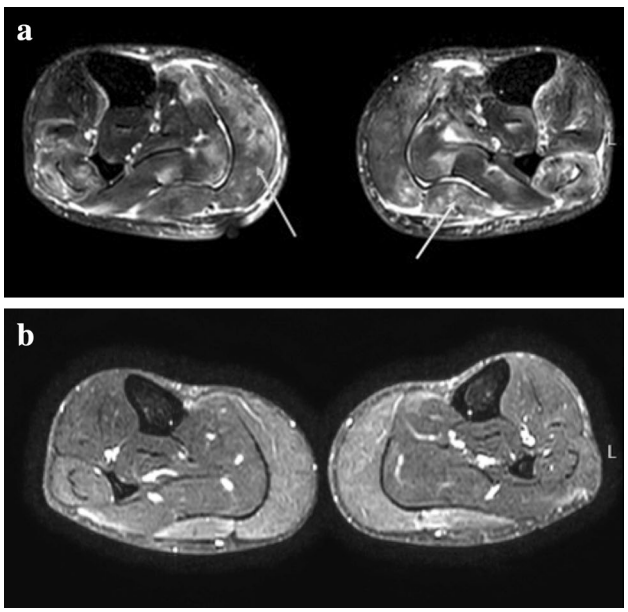

Fig. 3 **a** MRI showing severe myositis lesions of both lower legs in a patient with polyarteritis nodosa. **b** Follow-up MRI after 12 months of treatment with tocilizumab showing no more signs of myositis or vasculitis

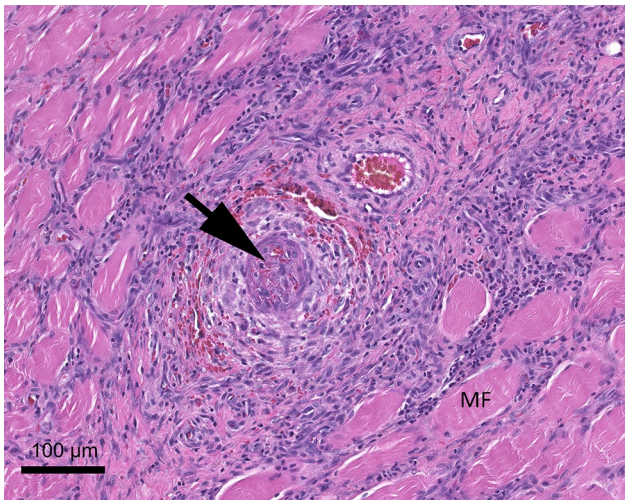

Fig. 4 Muscle biopsy (haematoxylin–eosin stain) showing necrotizing vasculitis of the epimysial arteries and arterioles with ischemic damages of the muscle tissue as a result of polyarteritis nodosa

PAN was confirmed. With respect to the patient's immunoglobulin deficiencies, genetic analyses excluded adenosine deaminase 2 deficiency [19].

As the disease flared after reduction of tocilizumab and there was previously a good therapeutic response to tocilizumab, we stopped intravenous immunoglobulin treatment and increased tocilizumab up to 800 mg iv every 4 weeks. This led to rapid clinical improvement and sustained remission, allowing glucocorticoids to be reduced to prednisolone 5 mg daily. His body weight normalized to 85 kg and CRP levels remained normal. Repeat electroneurography study performed 8 months after increasing the dose of tocilizumab showed a significant improvement of the sensorimotor neuropathy. MRI follow-up after 11 months of increased treatment revealed no signs of myositis (Fig. 3b). At his last follow-up, the patient has been in stable remission for 2 years on tocilizumab 800 mg iv every 4 weeks and 5 mg prednisolone daily. Apart from upper respiratory tract infections, no further side effects occurred during tocilizumab therapy. Figure 5 summarizes the clinical features and interventions of the present case.

Results of the literature search

The reported search strategy initially identified only 20 publications that were reviewed in full text and assessed for eligibility, of which 16 publications were excluded on the basis of the above-defined criteria. Finally, four articles (one case series and three case reports) describing the clinical effects of tocilizumab in PAN patients were included for further analysis. No additional studies were included from the screened reference lists.

In total, we report the clinical outcome of five cases from the literature (three adult cases, one paediatric case, and one adult case with PAN-associated amyloid A amyloidosis) and the present one. Table 1 displays the clinical, laboratory, imaging, and histological data and the therapy regime of these patients.

Overall, tocilizumab treatment was associated with clinical improvement in all patients over a period of at least 6 months (maximum: 50 months). Complete remission was achieved in 4 patients. Moreover, 3 patients were stable on a relatively low dose of daily prednisolone and 2 patients had no glucocorticoid treatment at last follow-up (minimum: 10 months).

Discussion

The patient described in this case report suffered from severe immobilizing polyneuropathy and myalgias associated with PAN. While other immunosuppressive approaches failed to control disease activity, increasing the dose of tocilizumab correlated with a rapid clinical improvement and sustained remission. Recent studies support the possible efficacy of tocilizumab in PAN. Saunier et al. [17] described three hepatitis B virus negative PAN patients with muscle involvement that were successfully treated with tocilizumab. Moreover, the use of tocilizumab resulted in sparing of glucocorticoids and other immunosuppressive drugs. Consistent with these findings, Watanabe et al. [15] presented another case of a paediatric patient with clinical improvement to tocilizumab and other immunosuppressive drugs. Furthermore, Hočevar et al. [14, 16] reported that tocilizumab could be a therapeutic option for PAN-associated amyloid A amyloidosis, a complication due to chronic inflammation.

Taken together, these results support the view that interleukin-6 signalling is involved in the pathogenesis of PAN. Nevertheless, more research is needed to prove this hypothesis. To our knowledge, only a small number of studies [8–10] directly address the role of interleukin-6 in PAN. All these studies found a correlation of interleukin-6 levels and disease activity. However, randomized-controlled clinical trials are needed to fully evaluate the safety and clinical efficacy of tocilizumab in order to determine its role in the clinical management of PAN. For example, Nozawa et al. [20] recently conducted a small pilot study of tocilizumab in four children with Kawasaki's disease, a medium-vessel vasculitis, that raises questions about possible side effects due to tocilizumab therapy in systemic vasculitis. In their study, the development of coronary-artery aneurysms in Kawasaki's disease was associated with tocilizumab therapy. To explain this apparently paradoxical observation, the authors refer to the concept of reparative inflammation [21]. However, the role of this emerging concept in PAN is unknown. As PAN

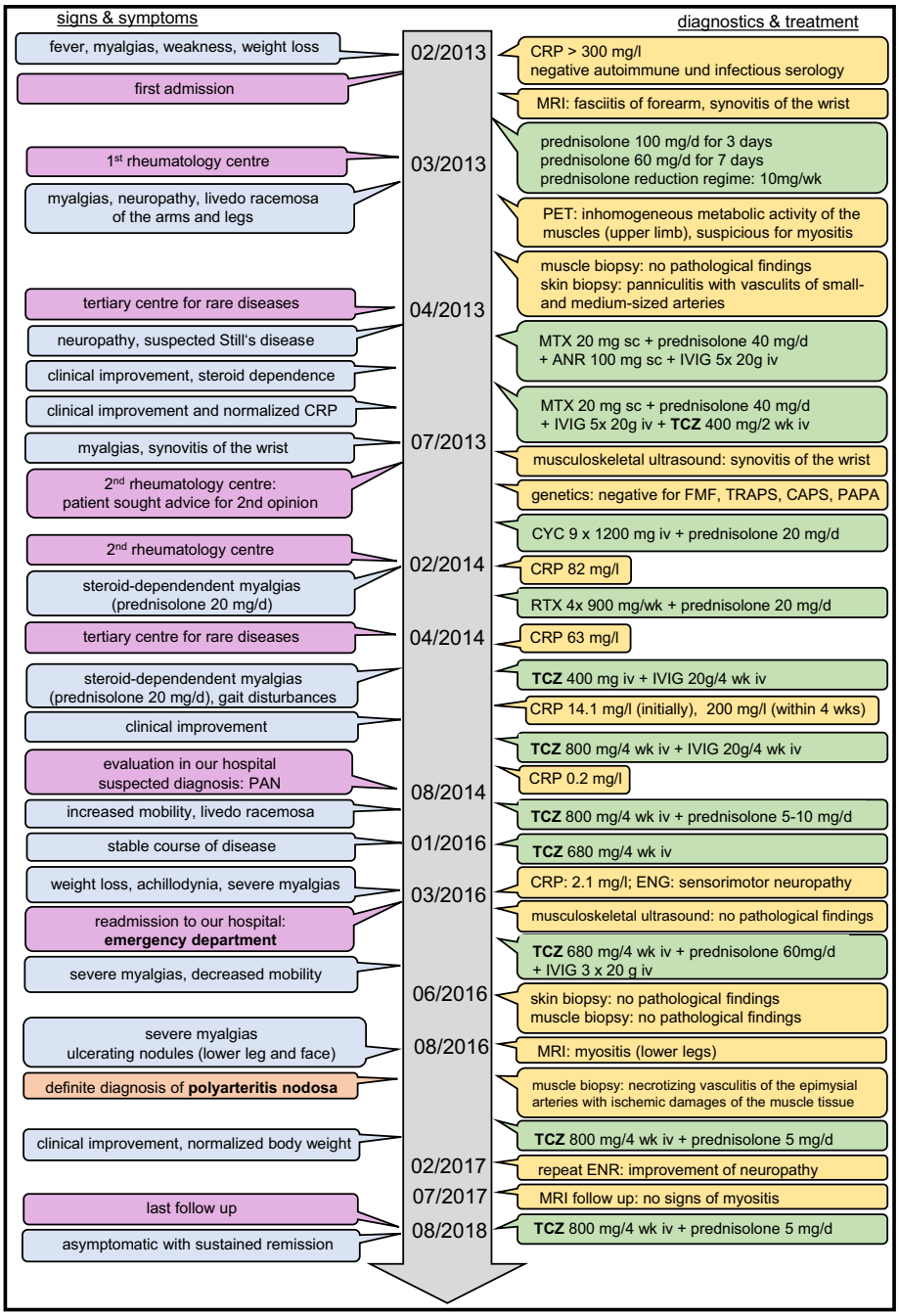

Fig. 5 Timeline of clinical features and interventions. *ANR* anakinra, *CAPS* cryopyrin-associated autoinflammatory syndromes, *CRP* C-reactive protein, *CYC* cyclophosphamide, *ENG* electroneurography, *IVIG* intravenous immunoglobulin, *FMF* Familial Mediterranean Fever, *MRI* magnet resonance imaging, *PAN* polyarteritis nodosa, *PAPA* pyogenic-arthritis-pyoderma-gangrenosum-acne-syndrome, *PET* positron emission tomography, *RTX* rituximab, *TCZ* tocilizumab, *TRAPS* tumor necrosis factor receptor-associated periodic syndrome, *wk* week

itself may be associated with coronary-artery aneurysms [22], the distinction between the potential side effects of tocilizumab therapy and the clinical manifestations of PAN may be difficult.

Finally, as it has been reported in the previous studies, anti-TNF therapy may be another promising option for patients with refractory PAN [3, 5]. For tocilizumab, anti-TNF therapy has not been systematically investigated in clinical trials in PAN and further research is required to evaluate the clinical effects of this approach and best therapy for refractory PAN.

Conclusion

Tocilizumab is a possible treatment option of refractory PAN. However, data from randomized-controlled trials are needed to evaluate the safety and clinical efficacy of tocilizumab in PAN.

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Compliance with ethical standards

Conflict of interest Martin Krusche reports receiving financial support from Chugai for an educational program and honorarium for a talk. Nikolas Ruffer declares that he has no conflict of interest. Ina Kötter reports receiving honorarium from Chugai and Roche for talks.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All authors fulfilled the ICMJE authorship criteria.

Informed consent Informed consent was obtained from the individual participant included in the study.

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