Review

Effectiveness and safety of tocilizumab in polyarteritis nodosa and adenosine deaminase 2 deficiency: a systematic literature review

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Received on July 13, 2025; accepted in revised form on September 16, 2025.

Clin Exp Rheumatol 2025.

Key words: adenosine deaminase 2 deficiency, polyarteritis nodosa, tocilizumab

Competing interests: none declared.

ABSTRACT

Objectives. *There is a significant need for medications that offer improved effectiveness and safety in the treatment of polyarteritis nodosa (PAN). Research has shown that serum interleukin-6 levels were elevated in both PAN and adenosine deaminase 2 deficiency (DADA 2) patients, which supported the exploration of tocilizumab for patients with refractory cases of these conditions.*

Methods. *A comprehensive systematic literature review was conducted to investigate the effectiveness and safety of tocilizumab in patients with PAN and DADA 2.*

Results. *We reviewed 28 studies. Twenty-nine PAN patients received tocilizumab, resulting in favourable response for twenty-two patients. Five patients did not respond to the treatment. Tocilizumab was discontinued in two patients due to adverse effects before its effectiveness could be evaluated. Fifteen DADA 2 patients were treated with tocilizumab, with two achieving complete response, two showing a partial response, and nine not responding at all. In two cases, the assessment of effectiveness was not possible. Three patients experienced ischaemic vascular events while on tocilizumab, and ten patients transitioned to anti-tumour necrosis factor therapies. Side effects included infections, cytopenias, and hyperlipidemia, which were consistent with those observed in other rheumatic disease treatments involving tocilizumab.*

Conclusion. *Tocilizumab appeared to be a promising and safe option for paediatric and adult PAN patients as a salvage therapy for those who did not respond to conventional and biologic immunosuppressive therapies. However, in patients with DADA 2, tocilizumab showed limited effectiveness and it generally performed worse than anti-tumour necrosis factor alpha agents in most cases.*

Introduction

Polyarteritis nodosa (PAN) is a systemic necrotising vasculitis primarily affecting medium-sized blood vessels, although it can also involve smaller vessels (1). It can impact various organs, including the skin, peripheral nervous system, gastrointestinal tract, and kidneys, while typically sparing the lungs (2). If not treated, PAN can pose significant risks to organ function and may even be life-threatening (3). The primary treatment for moderate to severe cases of polyarteritis nodosa involves glucocorticoids and cyclophosphamide (1, 2). Additionally, other conventional immunosuppressive agents such as azathioprine, methotrexate, mycophenolate mofetil, cyclosporine A, and tacrolimus may be used for maintaining remission (4, 5). However, the side effects associated with these conventional treatments can restrict their long-term use, and the disease often exhibits a relapsing nature. Consequently, there is a pressing need for more effective and safer therapeutic options for PAN (6). The success of biologic therapies in treating various rheumatic conditions offers rheumatologists a promising avenue to explore these agents for patients with PAN.

The low prevalence of PAN means that most insights into the effectiveness of biologic agents for treating this condition come from case reports and series. The primary experience with biologic treatments in PAN involves anti-tumour necrosis factor alpha (anti-TNF)

agents, specifically infliximab, adalimumab, and etanercept (5). Non-anti-TNF agents used in the treatment of PAN include the anti-CD20 antibody rituximab and the interleukin-6 receptor antagonist tocilizumab (5). Reports indicated that patients with both cutaneous and systemic forms of polyarteritis nodosa exhibited increased interleukin-6 activity (7, 8). One particular study suggested that elevated serum levels of interleukin-6 in PAN patients may be associated with disease activity (9). These findings support the rationale for targeting interleukin-6 signalling in PAN patients by using tocilizumab, which is the most widely employed IL-6 receptor antagonist in rheumatology practice (10, 11).

Adenosine deaminase 2 deficiency (DADA 2) is an autoinflammatory condition caused by biallelic mutations in the cat eye syndrome critical region candidate 1 (CECR1) gene, which closely mirrors the clinical manifestations of polyarteritis nodosa. Additionally, in one study a patient with DADA 2 exhibited elevated levels of interleukin-6 (12). Given the phenotypic similarities between these two disorders, many immunosuppressive treatments previously used for polyarteritis nodosa have also been explored for patients with DADA 2, including biologic therapies (13).

The potential involvement of increased interleukin 6 in the development of clinical features of PAN and DADA 2 has led healthcare professionals to try this agent in treating these conditions, particularly in cases that are refractory to standard therapies. The primary goal of this systematic literature review was to evaluate the effectiveness and safety of tocilizumab in patients with PAN and DADA 2. Our intention was to examine all documented cases in the literature that report the use of tocilizumab for treating PAN and DADA 2.

Methods

This systematic literature review was conducted in accordance with PRISMA guidelines (14). PRISMA Checklist is present in the Supplementary Materials section. This study was also registered in PROSPERO database of systematic review protocols with the ID number of CRD420251032183.

Information sources and eligibility criteria

A comprehensive literature review was performed using the Cochrane Database, MEDLINE (PubMed), Ovid, Scopus, and Web of Science. Studies published prior to January 1, 2025, were considered for inclusion, with no restrictions on language. All PAN and DADA 2 patients who received tocilizumab were included in the analysis. Additionally, relevant articles referenced in the collected literature were manually searched. Studies and case reports that did not provide information on the effectiveness of tocilizumab were excluded from the review. Abstracts lacking full texts were also omitted. Cases of polyarteritis nodosa that were HbsAg positive were also excluded, as their treatment protocols differed from those of other PAN patients.

Search strategy

The key words/items incorporated the MeSH term "polyarteritis nodosa" (MeSH Unique ID: D010488) along with the supplementary concepts of "adenosine deaminase 2 deficiency" (MeSH Unique ID: C000723487) and "tocilizumab" (MeSH Unique ID: C502936). Literature search algorithm is presented in the Supplementary Materials section.

Selection process, data collection process, data items

Initially, two reviewers (EST and SÇ) only reviewed the abstracts of all results. Following this review, they identified studies that met the criteria for screening. The full texts of the selected abstracts were then examined, and duplicates were removed to determine the eligible studies. After a final assessment and a discussion for studies that were not selected by both reviewers, a final decision was reached and the studies to be included were confirmed. The following data were collected from each of the chosen studies: the number of patients with PAN or DADA 2, the age and sex of each patient, interval between onset of PAN or DADA 2 and initiation of tocilizumab, clinical findings, affected organs and systems, laboratory parameters of the patients, CECR1 gene mutations in DADA 2 patients, previous treatments, dosage and administration route of tocilizumab, any concurrent immunosuppressive treatments with tocilizumab, the duration of tocilizumab therapy, the patients' responses to tocilizumab, and any side effects associated with the treatment. Response was defined using the terms "complete response", "partial response" and "lack of response". "Complete response" was defined as disappearance of clinical signs and symptoms, "Partial response" was defined as decrease in clinical signs and symptoms and "lack of response" was defined as continuation of clinical signs and symptoms in same or increased intensity and/or emergence of new clinical signs and symptoms. Due to tocilizumab's ability to normalise C-reactive protein (CRP) levels even in cases that do not clinically respond to this drug, acute phase reactants were not incorporated into these definitions.

Study risk of bias assessment, reporting bias assessment and certainty assessment

In light of the absence of randomised clinical trials and prospective studies, as well as the rarity of these diseases, this systematic literature review incorporated only case reports and case series. Due to the inherent characteristics of case reports and case series, assessments for risk of bias, reporting bias, and certainty could not be conducted.

Results

Study selection and study characteristics

Figure 1 illustrates the flowchart outlining the systematic literature review process. This review encompassed a total of 28 studies (10, 12, 15-40), all of which were either case reports or case series. Supplementary Table S1 presents the detailed characteristics of patients with polyarteritis nodosa who received tocilizumab (10, 15-29). Supplementary Table S2 reports the detailed characteristics of patients with adenosine deaminase 2 deficiency who

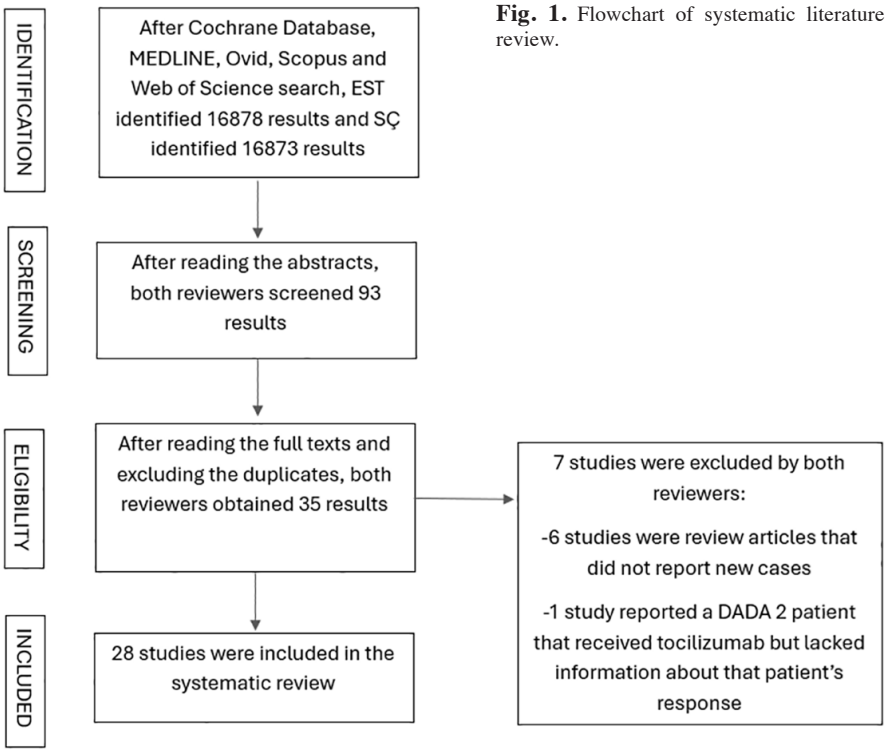

Fig. 1. Flowchart of systematic literature review.

were treated with tocilizumab (12, 30-40).

Effectiveness and safety of tocilizumab in polyarteritis nodosa patients

A total of 29 PAN patients were treated with tocilizumab. Table I summarises the demographic characteristics, clinical features and therapeutic features of these patients.

Eighteen patients achieved complete response with tocilizumab. Three patients responded to this agent, but exhibited residual symptoms: one experienced lingering dizziness, another had mild livedo, and the third reported residual arthralgia along with fewer fever episodes. One patient experienced a relapse of skin nodules and myalgia at the fourth month of treatment; however, after a temporary increase in glucocorticoid dosage, remission was restored, and the patient continued with tocilizumab. For the complete and partial responders, final CRP levels were recorded for seven patients, all of whom had CRP levels of ≤1 mg/L. Five patients did not respond to tocilizumab. In two cases, the treatment had to be halted due to adverse effects before its effectiveness could be evaluated. Glucocorticoids were completely discontinued in four patients, while six patients had their prednisolone dosage reduced to 5 mg/day. Additionally, one patient's prednisolone was lowered to 4 mg/day, and another patient's final prednisolone dose was 2.5 mg/day. In a study conducted by Hadjadj *et al*. ten patients with PAN received tocilizumab, resulting in a reduction of the median prednisolone dosage from 27.5 mg/day to 12.5 mg at three months, 8.5 mg at six months, and 5 mg at twelve months (29).

Out of 29 patients, 8 experienced side effects. One individual developed hyperlipidaemia, necessitating the start of statin therapy. Another patient suffered from upper respiratory tract infections, while a third exhibited mild neutropenia (with levels below 1500/microliter but above 1000/microliter), resulting in a temporary cessation of the medication for three months. The dosage of tocilizumab was reduced for three patients due to complications: one each for zoster infection, neutropenia, and thrombocytopenia. Additionally, tocilizumab was permanently discontinued in two patients, one due to a testicular abscess and the other due to deteriorating renal function.

Effectiveness and safety of tocilizumab in adenosine deaminase 2 deficiency patients

A total of 15 patients diagnosed with DADA 2 received tocilizumab. Table II summarises the demographic characteristics, clinical features and therapeutic features of these patients.

Among 15 DADA 2 patients, only two patients achieved complete response while being treated with tocilizumab. One of these individuals exhibited a phenotype similar to Castleman's disease, while the other patient was transitioned to infliximab despite being in remission to prevent potential vascular complications. Additionally, two patients demonstrated a partial response to tocilizumab. One of these patients was switched to adalimumab due to recurrent cerebral infarcts, resulting in a complete response. The other patient was transitioned to a treatment regimen that included steroids, tacrolimus, and adalimumab, to which he also responded completely. Conversely, nine patients did not respond to tocilizumab. Among these, three experienced vascular events while receiving tocilizumab: one suffered recurrent strokes, another had a right thalamic infarct along with right central retinal artery occlusion, and the third also experienced right central retinal artery occlusion. Six patients who did not respond to tocilizumab were subsequently placed on a regimen that included anti-TNF agents, all of whom showed favourable responses: two patients responded to etanercept monotherapy, two to adalimumab monotherapy, one to a combination of adalimumab and thalidomide, and one to a combination of adalimumab, methotrexate, and glucocorticoids. Two patients who did not respond to tocilizumab underwent allogeneic hematopoietic stem cell transplantation, resulting in complete responses. One patient who did not respond to tocilizumab passed away from necrotising pneumonia, although in the text, it remained unclear if he was under the immunosuppressive effects of tocilizumab at the time of pneumonia. The effectiveness of tocilizumab was not clearly established in two patients; one was switched to adalimumab after his

Table I. Demographic characteristics, clinical features and therapeutic features of polyarteritis nodosa patients treated with tocilizumab.

	Number of patients
Demographic features	5 paediatric patients (3 males, 2 females; median age: 8 years- ranging from 3 to 15 years), 24 adult patients (12 males, 10 females, in 2 patients sex was not specified; for 10 patients in 1 case series median age: 57 years, for 12 patients median age 37 years- ranging from 21 to 74 years)
Median interval from the onset of PAN symptoms to the commencement of tocilizumab treatment	12 months (1-120 months), this information was unavailable for 18 patients
Clinical Features	Constitutional symptoms (17 patients), arthralgia/arthritis (18 patients), myalgia (12 patients), myositis (5 patients), fasciitis (2 patients), skin involvement (10 patients), livedo racemosa (6 patients), subcutaneous nodules (6 patients), cutaneous ulcers (4 patients), finger ischaemia (2 patients), bullous skin lesion (1 patient), oral ulcer (1 patient), Kawasaki-like skin and mucosal lesions (1 patient) , renal involvement (6 patients), hypertension (2 patients), renal artery branch aneurysm (1 patient), gastrointestinal involvement (3 patients), intestinal perforation (1 patient), pulmonary involvement (2 patients) cardiac involvement (2 patients), coronary artery ectasia (1 patient), coronary artery aneurysm (1 patient), epididymoorchitis (1 patient), right arm aneurysm (1 patient), vertebral artery vasculitis (1 patient), peripheral nervous system involvement (11 patients), ocular involvement (5 patients), inner ear involvement (2 patients), biopsy proven AA amyloidosis (kidney and intestinal amyloidosis, 1 patient), clinical suspicion for amyloidosis (cardiac, 1 patient)
Previous treatment modalities	Glucocorticoids (26 patients), cyclophosphamide (16 patients), methotrexate (14 patients), IVIG (10 patients), azathioprine (8 patients), infliximab (4 patients), rituximab (3 patients), adalimumab (2 patients), anakinra (2 patients), dapsone (2 patients), etanercept (2 patients), mycophenolate mofetil (2 patients), mycophenolic acid (1 patient), cyclosporine A (1 patient), tacrolimus (1 patient), hydroxychloroquine (1 patient), colchicine (1 patient)
Median duration of tocilizumab treatment	12 months (6-50 months), this information was unavailable for 15 patients
Concomitant treatment with tocilizumab	17 patients received steroids, 3 patients received steroid+methotrexate, 1 patient received steroid+cyclophosphamide, 1 patient received steroid+azathioprine, 1 patient received steroid+ IVIG

IVIG: intravenous immunoglobulin; PAN: polyarteritis nodosa.

Table II. Demographic characteristics, clinical features and therapeutic features of adenosine deaminase 2 deficiency patients treated with tocilizumab.

	Number of patients
Demographic features	14 paediatric patients (7 males, 6 females, in 1 patient sex was not specified; median age 4.25- ranging from 0.5 to 17 years), 1 adult patient (male, 22 years old)
Median interval from the onset of DADA 2 symptoms to the commencement of tocilizumab treatment	2.5 months (1-10 months), this information was unavailable for 11 patients
Clinical features	Fever (10 patients), livedo reticularis (6 patients), livedo racemosa (1 patient), rash (4 patients), erythema nodosum (4 patients), erythematous macule (2 patients), necrotic ulcer (1 patient), aphthous lesion (1 patient), arthralgia/arthritis (8 patients), myalgia (1 patient), haemorrhagic stroke (4 patients), ischaemic stroke (4 patients), intracranial haemorrhage (2 patients), central nervous system microbleed (1 patient), abnormal gait (1 patient), diplopia (1 patient), peripheral facial nerve palsy (1 patient), strabismus (1 patient), intestinal perforation (2 patients), hypertension (2 patients), renal infarction (1 patient), testicular thrombosis (1 patient), colitis (1 patient), pancreatitis (1 patient),Castleman disease-like phenotype (2 patients), hepatomegaly (4 patients), splenomegaly (3 patients), hypogammaglobulinemia (5 patients), hypergammaglobulinemia (1 patient), anaemia (5 patients), thrombocytosis (2 patients), lymphopenia (2 patients), leukopenia (1 patient), biopsy proven AA amyloidosis (renal and intestinal, 1 patient)
Previous treatment modalities	Glucocorticoids (12 patients), IVIG (6 patients), methotrexate (6 patients), cyclophosphamide (3 patients), cyclosporine A (2 patients), azathioprine (1 patient), thalidomide (1 patient), colchicine (1 patient)
Median duration of tocilizumab treatment	7 months (2 to 48 months), this information was unavailable for 10 patients
Concomitant treatments with tocilizumab	5 patients received steroids, 1 patient received a combination of steroids and methotrexate, this information was unavailable for 9 patients

DADA 2: adenosine deaminase 2 deficiency; IVIG: intravenous immunoglobulin.

sibling, also diagnosed with DADA 2, experienced a stroke while on tocilizumab. The second patient developed central nervous system microbleeds and testicular thrombosis, but it was uncertain whether he continued receiving tocilizumab during these incidents. In most patients with DADA 2, tocilizumab did not result in reported side effects. One patient experienced severe hypertension; however, tocilizumab treatment was continued alongside antihypertensive medications. When this patient also suffered from intestinal perforation, the use of tocilizumab was permanently halted. Initially, the authors attributed these complications to tocilizumab, but they later reconsidered this view, suggesting that these events might stem from a different diagnosis. This led them to investigate CECR1 mutations, which ultimately confirmed the DADA 2 diagnosis. Whether tocilizumab contributed to these adverse events remained unclear. Additionally, one patient who did not respond to tocilizumab succumbed to necrotizing pneumonia, but it was unclear if he was experiencing the immunosuppressive effects of tocilizumab at that time.

Discussion

Recent studies on diagnostic and treatment modalities in vasculitides generally focused on large vessel vasculitides (primarily giant cell arteritis and Takayasu's arteritis) and small vessel vasculitides, mainly antineutrophil cytoplasmic antibody vasculitides (41, 42). Studies on medium vessel vasculitides, mainly on polyarteritis nodosa were less common due to the rarity of this condition. Therefore, there is an unmet need for large scale studies for new and alternative treatment modalities for PAN and related conditions. This review assembled all the available data on the use of tocilizumab in PAN and DADA 2 patients. Data obtained in this review demonstrated that tocilizumab may be beneficial for both adult and paediatric patients with polyarteritis nodosa (PAN), serving as an alternative for those who did not respond adequately to various conventional and/or biologic immunosuppressive therapies. In contrast, the majority of patients with DADA 2 showed insufficient response to tocilizumab. The safety profile of the medication was found to be acceptable in both conditions.

The inhibition of the interleukin-6 pathway using tocilizumab is becoming increasingly prevalent in the treatment of various rheumatic diseases, such as rheumatoid arthritis (43), adult-onset Still's disease (44), giant cell arteritis (45), Takayasu's arteritis (46), Behçet's disease (47) and systemic sclerosis (48). This review investigated the potential of this biologic agent as a viable treatment option for patients with polyarteritis nodosa and adenosine deaminase 2 deficiency. It represented the most comprehensive analysis of tocilizumab's application in both polyarteritis nodosa and DADA 2 patients. Prior reviews by Conticini *et al*. (5) and Akiyama *et al*. (49) documented the effectiveness and safety of tocilizumab in 12 and 11 patients with polyarteritis nodosa respectively. In contrast, our review encompassed 29 PAN patients who were treated with tocilizumab. Additionally, the review by Zhang *et al*. highlighted 10 DADA 2 patients who received tocilizumab (50), while Maccora *et al*. reported on 9 DADA 2 patients treated with the tocilizumab (51). Our review includes a total of 15 DADA 2 patients who received tocilizumab.

Table III comparatively demonstrates the effectiveness and safety of tocilizumab in PAN and DADA 2 patients in our review. The majority of patients with polyarteritis nodosa (PAN) included in this review exhibited a positive response to tocilizumab, with a combined total of 75.8% achieving either a complete or partial response. Tocilizumab proved effective for individuals who did not respond sufficiently to standard immunosuppressive therapies. Additionally, it was beneficial for patients who had previously been treated with other biologic therapies, including anti-TNF agents, rituximab, and anakinra. This medication was also used as a first-line treatment in two patients, one diagnosed with cutaneous PAN (10, 26) and the other with AA amyloidosis secondary to PAN (19, 20). Given the significant role of interleukin 6 in the C-reactive protein (CRP) response (52), tocilizumab successfully normalised CRP levels in these patients, consistent with its effects observed in other clinical contexts (53, 54). Despite these promising outcomes, the rates of complete and partial responses in our review were somewhat lower than those reported by Akiyama *et al*. who noted a clinical response in all 11 PAN patients treated with tocilizumab (49), and by Conticini *et al*. who found a complete or partial response in 91.7% in 12 PAN patients that received tocilizumab (5). Akiyama *et al*. concluded that tocilizumab was effective for patients with refractory or relapsing PAN and could reduce the need for glucocorticoids (49), while Conticini *et al*. proposed that tocilizumab may serve as a third or fourth-line treatment option for PAN patients (5). Although these findings are encouraging, it is important to remain cautious regarding the potential for "publication bias," as there is a tendency for studies with positive results to be published more frequently (28, 49).

In contrast to the positive results profile observed in PAN, the results regarding the effectiveness of tocilizumab in patients with DADA 2 were disappointing. Tocilizumab was effective in a DADA 2 patient whose clinical presentation was similar to that of Castleman disease, where this treatment is recognised as a first-line therapy (55). However, tocilizumab failed to prevent vascular events in multiple patients, leading to 10 out of the 15 DADA 2 patients in this review to transition to anti-TNF agents, which successfully induced remission in all of them. Our findings aligned with the review by Conticini *et al*. which reported ineffectiveness of tocilizumab in four DADA 2 patients (5), and with the review by Maccora *et al*. where only one out of nine DADA 2 patients responded positively to tocilizumab (49). Most DADA 2 patients in our study subsequently received anti-TNF agents, which proved to be effective. A notable observation in DADA 2 patients is the significant release of TNF-α from M1 macrophages and neutrophil extracellular traps (56). Given the critical role of TNF-α in the pathogenesis of DADA 2, anti-TNF agents are preferred bio-

Table III. Summary comparing the effectiveness and safety of tocilizumab in polyarteritis nodosa and adenosine deaminase 2 deficiency patients.

	Polyarteritis nodosa	Adenosine deaminase 2 deficiency
Total number of patients	29	15
Number of patients with complete response	19	2
Number of patients with partial response	3	2
Number of patients with lack of response	5	9
Number of patients where effectiveness of tocilizumab is not clear	0	2
Number of patients who discontinued tocilizumab before assessment of efficacy	2	0
Number of patients that experienced side effects	8	2*
Number of patients discontinuing tocilizumab due to side effects	2	1*
List of side effects	Hyperlipidaemia requiring statin, upper respiratory tract infection, mild neutropenia (drug temporally ceased), herpes zoster infection (leading to dose reduction), neutropenia (leading to dose reduction), thrombocytopenia (leading to dose reduction), testicular abscess (drug permanently stopped), renal dysfunction (drug permanently stopped)	*One patient suffered from necrotising pneumonia, but it is not clear if this occurred in a time period close to tocilizumab use. *Hypertension and intestinal perforation in one patient. Initially, the authors attributed these complications to tocilizumab, but they later reconsidered this view, suggesting that the events might stem from a different diagnosis, which ultimately lead to adenosine deaminase 2 deficiency.

Table IV. Limitations of this systematic literature review.

- Evidence quality from the studies was considered low, as all included studies were either case reports or case series, which were inherently limited by selection bias and lack of standardised outcome measures. Due to this nature of the included studies, assessments for risk of bias, reporting bias, and certainty could not be performed
- Although it represented the most comprehensive review on this topic, the overall patient count remained limited. This small sample size was attributed to the rarity of these conditions and to the fact that only a minority of PAN and DADA 2 patients received tocilizumab, which was utilised "off-label" for both conditions.
- The variability in clinical manifestations among patients with the same diseases complicated the analysis (for example some PAN patients had only cutaneous manifestations, some patients had visceral involvement, some had accompanying AA amyloidosis; likewise, some DADA 2 patients had a phenotype resembling Castleman disease, some patients had visceral abdominal involvement and many other patients had recurrent cerebrovascular events.)
- Treatment approaches varied significantly; some clinicians combined tocilizumab with steroids and conventional immunosuppressives, while others used it in combination with steroids. Most practitioners administered tocilizumab as a second or third-line treatment, although in two cases of PAN, it was given as a first-line option. Differences in duration of tocilizumab treatment, in dosage and administration route (intravenous or subcutaneous) of tocilizumab created further heterogeneity.
- Lack of follow-up data and information regarding the long-term side effects of tocilizumab in these patients was another limitation.

logic therapies for preventing vascular events and managing vasculitic symptoms these patients (57, 58). Despite the similarities in their clinical presentation, patients with PAN and DADA 2 exhibited differing responses to tocilizumab, as noted in the review by Conticini *et al*. (5). This discrepancy suggests that the underlying pathophysiology of these diseases may differ, indicating that while interleukin-6 may significantly contribute to the pathogenesis of PAN, its role may not be as critical in DADA 2.

The side effects associated with tocilizumab in patients with PAN and DADA 2 were consistent with those observed in other rheumatic conditions, including rheumatoid arthritis, giant cell arteritis, adult-onset Still's disease, and systemic sclerosis (59-63). It is important to note, however, that the case reports and series included in this review documented side effects over a limited time frame, and the long-term effects of tocilizumab in these specific patient populations remains largely unknown. Consequently, while tocilizumab appeared to be a safe option for treating PAN and DADA 2 patients, clinicians must remain vigilant regarding potential side effects, such as infections, as well as the specific risks associated with tocilizumab use, including dyslipidaemia and visceral perforation.

This review had several limitations. These were inclusion of only case reports and case series- which lacked standardisation and were open to bias, relatively small number of PAN and DADA 2 patients, heterogeneity among clinical features of PAN and DADA 2 patients, heterogeneity in treatment strategies and lack of long-term safety data for tocilizumab. These limitations are further elaborated in Table IV.

Mechanistic insights

In contrast to the positive outcomes reported in most PAN patients treated with tocilizumab, Rimar *et al*. documented two instances in which tocilizumab was ineffective for two patients with polyarteritis nodosa (PAN) (22, 28). The authors noted elevated levels of phosphorylated signal transducers and activators of transcription 3 (STAT 3) specifically in the CD4+ and CD8+

T cell subsets of one patient. They proposed that the redundancy within the signalling system, along with the activation of the Janus kinase-signal transducers and activators of transcription 3 (JAK-STAT3) pathway through mechanisms that circumvented the IL-6 pathway, such as stimulation via toll-like receptors 4, 7, or 9, and IL-23, might account for the positive response to tofacitinib, which targeted downstream effects, rather than tocilizumab in that particular case (28). Although tocilizumab was generally effective in PAN patients in this review, caution is advised, as varying signal transduction pathways and cytokine profiles may predominate in individual patients, potentially leading to differing responses to various targeted treatment modalities, including interleukin-6 receptor antagonism with tocilizumab.

Conclusions

In summary, this systematic literature review demonstrated that tocilizumab appeared to be an effective option that reduced the need for steroids in both paediatric and adult PAN patients who did not respond to standard immunosuppressive therapies or biologic treatments. In patients with DADA2, while tocilizumab improved in certain clinical and laboratory indicators of systemic inflammation and could be beneficial for those with a phenotype similar to Castleman's disease; overall it was not effective and was unable to prevent the onset or progression of ischaemic vascular events. Consequently, it was generally less preferred compared to anti-TNF agents for most DADA 2 patients. In both PAN and DADA 2 patients tocilizumab had an acceptable safety profile that was consistent with the other rheumatic diseases where this drug was utilised. Large-scale randomised controlled trials of tocilizumab in PAN patients are essential to draw definitive conclusions and to clarify its position within the treatment framework for PAN. Additionally, research aimed at identifying specific subgroups of PAN patients who are more likely to benefit from interleukin-6 pathway blockade will significantly assist clinicians in their treatment decisions.

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