Egyptian Rheumatology and Rehabilitation

CASE REPORT

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Successful treatment of AA amyloidosis with tocilizumab, resulting in the disappearance of amyloid deposits: a case-based review

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Abstract

Background AA amyloidosis is a multisystem disease characterized by the deposition of serum amyloid A protein, which is secondary to chronic inflammation. Tocilizumab (an interleukin-6 inhibitor monoclonal antibody) was effective in suppressing inflammation, normalizing serum amyloid A protein levels, and inducing remission in patients with amyloidosis. Recently, tocilizumab treatment has been associated with the disappearance of amyloid deposits.

Case presentation A 61-year-old woman was referred to our hospital in 2011 due to oligoarthritis of both knees and elevation of acute-phase reactants. Corticosteroids and methotrexate were prescribed for the possibility of polymyalgia rheumatica, without clinical response. Two years later, the patient presented with foamy urine, nocturia, sweating, and dizziness. An elevated C-reactive protein (CRP), erythrocyte sedimentation rate, and nephrotic-range proteinuria were found. Autoantibodies and complements levels were normal. No signs of acute infections or cardiovascular disease were evidenced and amyloidosis was suspected. Rectal and oral mucosa biopsies were performed and amyloid AA deposits were detected in both. Magnetic resonance imaging (MRI) of the right knee showed arthropathy due to amyloid deposition. Intravenous monthly tocilizumab was prescribed with rapid improvement of CRP, proteinuria, and nephrotic syndrome symptoms. Arthritis also improved significantly. Two years later, a new biopsy of the rectal mucosa did not show amyloid deposits and the right knee MRI was normal, without evidence of amyloid synovitis. In 2017, isotopic synoviorthesis of both knees was performed due to repeated episodes of arthritis. Eight years after the start of Tocilizumab, the patient continues treatment and remains clinically stable, with no evidence of recurrence.

Conclusions Tocilizumab treatment controls chronic inflammatory disease and improves symptoms of AA amyloidosis. According to the latest evidence, long-term treatment with tocilizumab may remove amyloid deposits from tissues, leading to a definitive cure for this disease. To our knowledge, this is the first case of regression of amyloid deposits both in biopsy and magnetic resonance after treatment with tocilizumab.

Keywords Amyloid A amyloidosis, Serum amyloid A protein, Nephrotic syndrome, Oligoarthritis, IL-6 inhibitor, Tocilizumab

Introduction

AA amyloidosis is a multisystemic disorder characterized by the extracellular deposition of fibrils derived from serum amyloid A (SAA) protein. SAA protein is synthesized by hepatocytes under the regulation of proinflammatory cytokines, particularly interleukin(IL)-6, but also tumor necrosis factor (TNF) and IL-1. A chronically high plasma concentration of SAA results in the aggregation

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of amyloid into cross-β-sheet fibrillar deposits. Therefore, amyloid production and deposition are associated with chronic inflammation, usually secondary to infections (tuberculosis), inflammatory disorders especially rheumatoid arthritis (RA), or some tumors such as renal carcinoma and Castleman's disease [1, 2].

Amyloid deposition occurs in all tissues of the human body. However, the kidneys are most frequently involved, with proteinuria as a first clinical manifestation in almost 95% of patients. Around 50% of patients present with nephrotic syndrome, which can lead to end-stage renal failure [1, 3].

Biopsy is considered the gold standard for diagnosis and samples are usually taken from abdominal fat, kidney, oral mucosa, rectal mucosa, or bone marrow. Amyloid appears deep red on light microscopy and shows apple-green birefringence under polarized light following Congo red staining [1, 2]. Immunohistochemistry may specifically reveal AA protein in the deposits.

Current AA amyloid treatment is based on the control of the inflammatory response associated with the underlying disease. Since amyloid protein has considerable resistance to degradation because of its β-sheet structure [1, 2], the primary goal of therapy has been normalizing SAA protein levels, not clearing the already existing amyloid deposits [1, 2, 4]. However, novel therapies are showing promising results in the dissolution of amyloid protein deposits [1, 2, 4] and among these, tocilizumab seems to be the most effective [5, 6].

In this report, we describe a case of AA amyloidosis with clinical remission and disappearance of amyloid deposits after tocilizumab treatment and present a literature review.

Case presentation

A 61-year-old overweight Caucasic woman with a history of hypothyroidism treated with levothyroxine, presented in our Rheumatology clinic in September 2011 with acute inflammatory pain in the cervical region, shoulders, and hips, functional limitation of the shoulder and pelvic girdle and knee swelling. Polymyalgia rheumatica was suspected. Laboratory tests showed an elevation of acute-phase reactants with an erythrocyte sedimentation rate (ESR) of 96 mm/h (reference range 0–20) and a C-Reactive protein (CRP) of 225 mg/L (reference range 0–5). Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, antinuclear antibodies, extractable nucleus antibodies, anti-neutrophil cytoplasmic antibodies, viral serologies (hepatitis B virus, hepatitis C virus, human immunodeficiency virus), and HLA-B27 were negative. Immunoglobulins and complement levels were normal.

Corticosteroids, up to 30 mg/day, were prescribed, with minimal clinical improvement and persistent elevation of acute-phase reactants. Serum tumor markers and whole-body computed tomography (CT) showed no significant findings. Temporal artery ultrasound and temporal artery biopsy were negative. Panendoscopy and PET-CT revealed no relevant findings.

Several knee arthrocentesis were performed. The synovial fluid had inflammatory characteristics (5000–12,000 leucocytes/microliter) and no crystals were visualized by optical microscopy. Joint symptoms improved after local infiltration of triamcinolone but rapidly recurred, so treatment with subcutaneous methotrexate up to 15 mg weekly was prescribed. A year later, due to a lack of improvement, methotrexate was withdrawn.

After 2 years with arthritis and elevated acute phase reactants, the patient referred new onset of nausea, epigastric pain, alternating constipation and diarrhea, foamy urine, nocturia, sweating, and dizziness. Laboratory tests showed an ESR of 123 mm/h (reference range 0–20), CRP 192 mg/L (reference range 0–5), and proteinuria that increased rapidly until it reached the nephrotic range (peak proteinuria/creatinuria 9992 mg/g in February 2014, reference range < 500). Normal renal function was maintained. Autoantibodies and complements levels were normal. No signs of acute infections or cardiovascular disease were evidenced and amyloidosis was suspected. Rectal and oral mucosa biopsies were preferred over renal biopsy due to the lower risk of complications. Deposits of amorphous eosinophilic material which stained deep red with Congo Red were detected in both. Immunohistochemistry demonstrated that AA protein was present in the deposits, and systemic amyloidosis was diagnosed (Fig. 1). The Mantoux test was negative. Whole-body scintigraphy, electromyogram and echocardiogram revealed no significant findings. In a repeat whole-body CT no abnormalities were visualized. Magnetic resonance imaging (MRI) of the right knee was performed with findings suggestive of amyloid arthropathy (Fig. 2).

Due to the persistence of inflammatory arthritis of the knee (not meeting the criteria for RA) and the diagnosis of secondary amyloidosis, intravenous tocilizumab 8 mg/kg every 4 weeks was initiated in March 2014 and prednisone 10 mg/day was maintained.

In the following months, progressive improvement in symptoms and a rapid decrease in ESR, CRP, and proteinuria (Fig. 3) were noted. Twelve months after the start of tocilizumab, the patient had proteinuria/creatinuria values < 3000 mg/g. At 24 months, proteinuria had completely disappeared.

SAA protein was not measured in the pre-tocilizumab phase. Following the initiation of tocilizumab, SAA protein was measured repeatedly. Values were always under

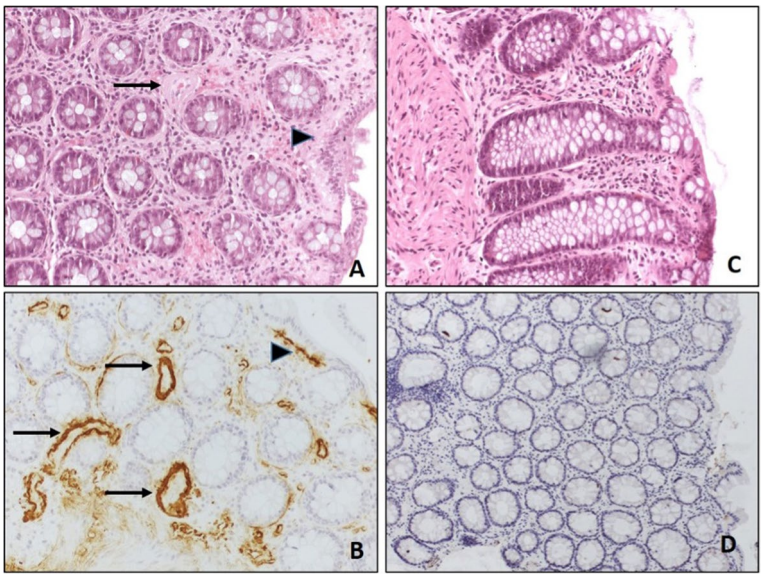

Fig. 1 Rectal biopsies prior to tocilizumab treatment (**A**, **B**) and after 2 years of treatment (**C**, **D**). With HE stain (**A**), tiny eosinophilic deposits in vascular vessels of the lamina propria (arrow) and superficial area (arrowhead) are intensely highlighted with AA-protein immunohistochemistry (**B**). No deposits were found either with HE (**C**) or following immnunohistochemical procedures (**D**) after treatment

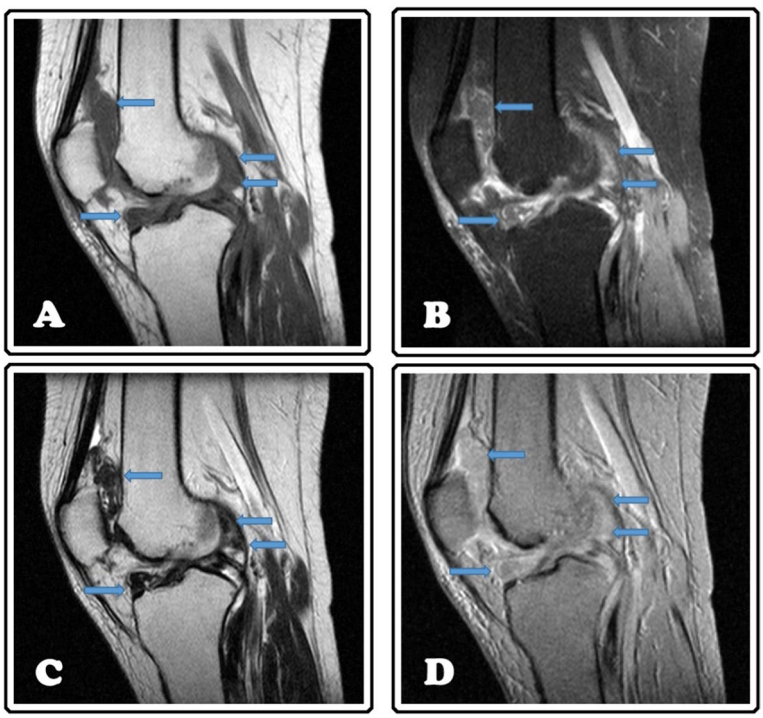

Fig. 2 MRI pretreatment. Sagittal T1-w fast spin echo (FSE) image (**A**), fat-suppressed proton density (FS PD) FSE image (**B**), T2-w FSE image (**C**), and T2-w gradient recalled echo (GRE) image (**D**). In the articular recesses, a thickening of the synovium is identified, with multiple nodules isointense to the muscle in T1-w FSE and FS PD-w FSE, hypointense in T2-w FSE and without signal loss in T2-w GRE, in relation to amyloid deposits (arrows). Joint effusion is also found

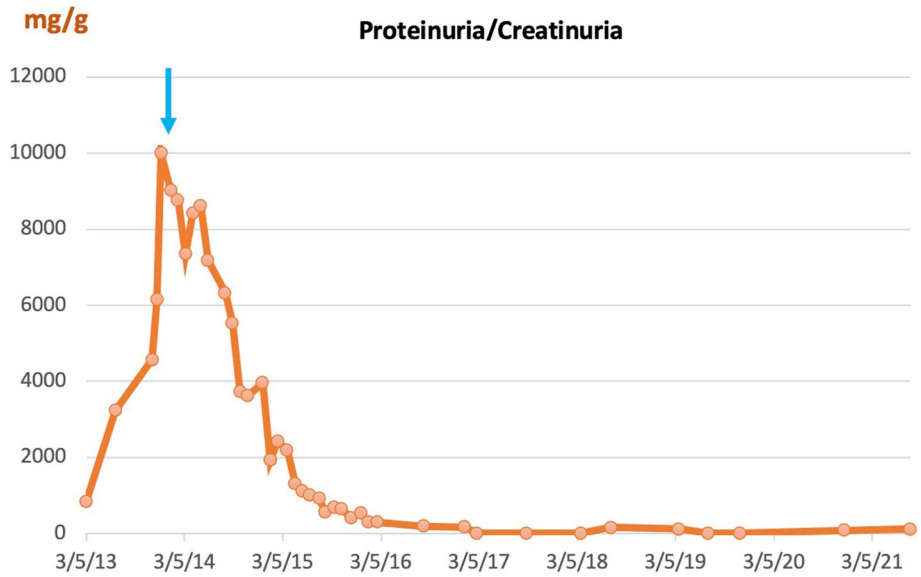

Fig. 3 Proteinuria/creatinuria over time. Blue arrow: start of tocilizumab

10 mg/L with a progressive decrease until levels < 1 mg/L were detected after 1 year of treatment.

A right knee MRI performed 4 months after starting tocilizumab showed a significant decrease in the size and number of amyloid deposits (Fig. 4). In January 2016, a follow-up MRI showed complete disappearance of amyloid deposits (Fig. 5).

Two years after the initial biopsy, a follow-up rectal mucosa biopsy did not reveal amyloid deposits or AA protein positivity (Fig. 1).

Despite the favorable response of the amyloid deposits and kidney involvement, the patient maintained repeated episodes of mild knee arthritis. Isotopic synoviorthesis was therefore performed on both knees in 2017, leading to a decrease in the frequency of flare-ups.

Currently, 8 years after the diagnosis of AA amyloidosis, the patient is receiving treatment with subcutaneous tocilizumab 162 mg every 9 days only. No clinical flare-ups have been documented in the last 5 years. Acute phase reactants remain within the normal range and no recurrence of proteinuria has been observed. Serum amyloid A protein has remained < 1.0 mg/L since March 2015.

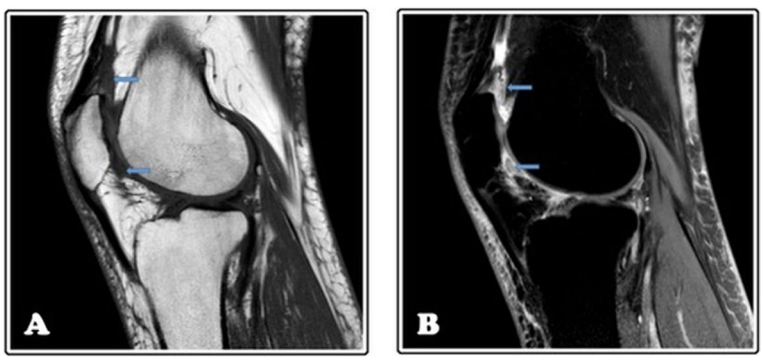

Fig. 4 MRI after 4 months of treatment with tocilizumab. Sagittal T1-w FSE image (**A**) and FS PD-w FSE image (**B**). In the joint recesses, a thickening of the synovium is identified with a significant decrease in the size and number of amyloid deposits. In the superior hoffatic and suprapatellar recesses, a nodule isointense to the muscle persists on T1-w FSE and FS PD-w FSE (arrows). Joint effusion is also found

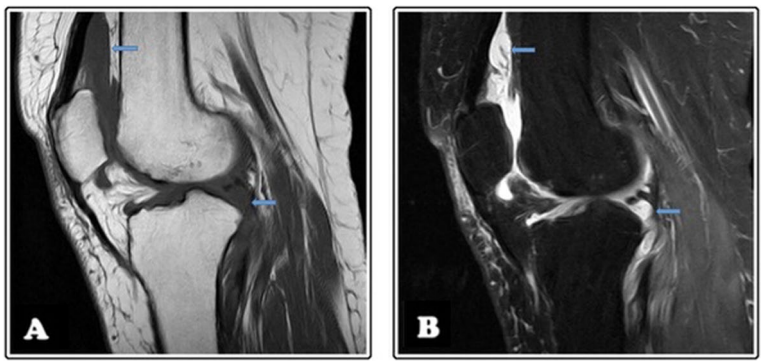

Fig. 5 MRI after 22 months of treatment with tocilizumab. Sagittal T1-w FSE image (**A**) and FS PD-w FSE image (**B**). Complete disappearance of amyloid deposits. Only mild synovial thickening and effusion are seen (arrows)

Discussion and literature review

To our knowledge, this is the first case of the disappearance of amyloid deposits both in biopsy and magnetic resonance images after treatment with tocilizumab.

The association of AA amyloidosis with rheumatic diseases has been extensively described, especially for RA. Currently, the incidence of amyloidosis in these pathologies is decreasing, due to better control of inflammation at the onset of the disease and the availability of new therapies such as biological drugs [1, 3].

The serum concentration of SAA closely reflects the activity of chronic inflammatory diseases [7]. The median plasma concentration of SAA in healthy people is less than 3 mg/L and can increase to more than 1000 mg/mL during an acute-phase response [8]. Targeted anti-inflammatory treatment aimed at promoting a sustained and complete normalization of circulating SAA levels prevents progressive amyloid deposition and protects renal function [1]. Gillmore et al. [7] reported that in AA amyloidosis, when SAA concentrations were less than 10 mg/L, the levels of amyloid deposits in the organs decreased and survival improved to 90% at 10 years versus 40% at 10 years in patients with SAA levels of 10 mg/L or higher.

Conventional disease-modifying agents (azathioprine, cyclosporine, cyclophosphamide, and corticosteroids) did not achieve a satisfactory suppression of SAA levels in many active cases. TNF inhibitors and abatacept reduce SAA levels, but complete normalization is rare, and clinical response is not always evidenced [4, 9].

Of the drugs used in arthritis-related AA amyloidosis, tocilizumab (an IL-6 receptor monoclonal antibody) has been associated with the best clinical outcomes. It not only improves all clinical features of AA amyloidosis but also normalizes SAA levels and can lead to a reduction of the deposits [10]. A comparison of the efficacy of tocilizumab, anti-TNF, and other biological therapies, showed a greater utility of tocilizumab [5, 6].

The terms "tocilizumab" [Supplementary Concept] and "amyloidosis" [Mesh] were used in PubMed identifying 50 references in the English/Spanish literature, published from September 2006 to September 2022. Articles with no full text and review articles with no new cases were not included. Cases of AA amyloidosis not related to rheumatic diseases were excluded. We completed the search manually, finding 4 additional case reports about tocilizumab in AA amyloidosis secondary to rheumatic diseases. Finally, we selected 35 cases for detailed review [11–46] as represented in Fig. 6. The efficacy of tocilizumab has been described principally in patients with RA [11–26], but also in AA amyloidosis secondary to systemic juvenile idiopathic arthritis [26–30], familial Mediterranean fever [31–36] psoriatic arthritis [26, 37, 38], ankylosing spondylitis [39], Still's disease [40], Muckle-Wells syndrome [41], Behçet's syndrome [42–44], polyarteritis nodosa [45], and Takayasu arteritis [46]. Some of the studies report a long-term efficacy [12, 18, 32, 34, 35, 37, 39, 41, 47] of up to 9 years.

In 11 case reports of patients treated with tocilizumab [10, 12–14, 21, 25, 29, 33, 34, 40, 45] a follow-up biopsy was performed and a reduction or disappearance of the deposits was also observed. Lane et al. [10] analyzed pre- and on-treatment serial scintigraphy scans in 20 patients with AA amyloidosis, showing that AA amyloid deposits either regressed or did not increase whilst on tocilizumab. We have not identified other studies demonstrating the disappearance of amyloid arthropathy in MR images.

An important factor that may contribute to the efficacy of tocilizumab is the early administration after the diagnosis of amyloidosis [4, 46]. In our case, tocilizumab was started 4 months after the onset of nephrotic-range proteinuria.

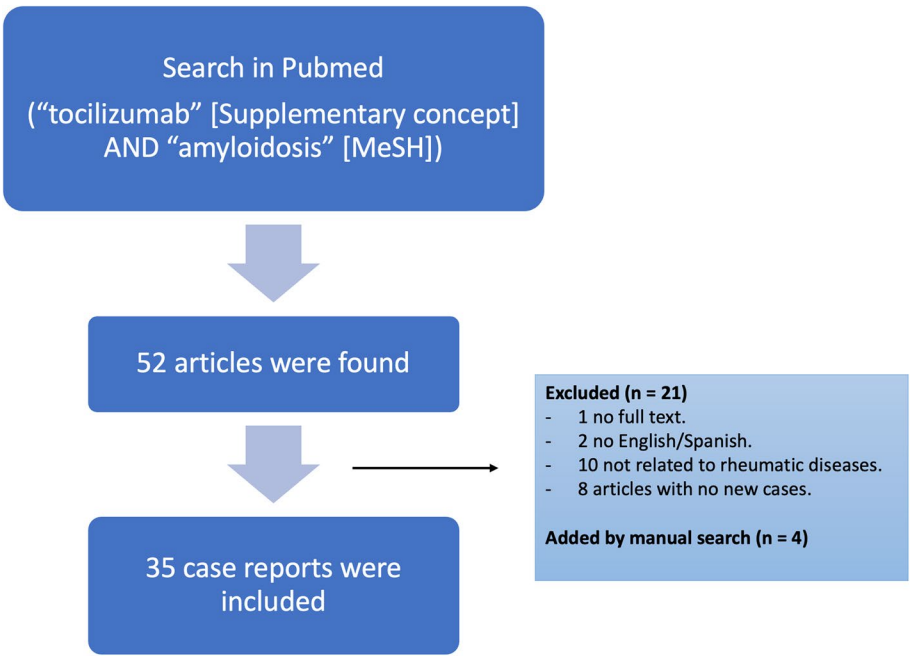

Fig. 6 Search strategy for review of the literature

Conclusions

In conclusion, we present a patient with chronic seronegative oligoarthritis and secondary AA amyloidosis successfully treated with tocilizumab, with the disappearance of the amyloid deposits in the rectal biopsy. Amyloid often accumulates in the tissue in a patchy form, but the regression of the deposits was also evidenced in the articular MRI. We have reviewed the prior evidence, and we have found eleven case reports that describe a reduction of the deposits in biopsy, but none have demonstrated total nor partial disappearance of amyloid arthropathy in MRI. To our knowledge, this is the first case of regression of amyloid deposits both in biopsy and MRI after treatment with tocilizumab. The fact that the clearance of the deposits is possible indicates we should aim for a definitive cure for this disease, not only to control the inflammation.

Abbreviations

CRP	C-reactive protein
CT	Computed tomography
ESR	Erythrocyte sedimentation rate
FSE	Fast spin echo
FS PD	Fat suppressed proton density
GRE	Gradient recalled echo
IL	Interleukin
MRI	Magnetic resonance imaging
RA	Rheumatoid arthritis
SAA	Serum amyloid A
TNF	Tumor necrosis factor

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Not applicable.

Authors' contributions

MTC and JBC analyzed and interpreted the patient data. MTC reviewed the previous literature and was the major contributor to writing the manuscript. JAB examined the MRIs, made the report, and provided the images. CP performed the histological examination of the rectal and oral mucosa biopsies, made the report, and provided the images. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approved by Ramón y Cajal University Hospital ethics committee; reference number 043/16.

Consent for publication

The patient gave her informed consent prior to her inclusion in the report.

Competing interests

The authors declare that they have no competing interests.

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References

1. Papa R, Lachmann HJ (2018) Secondary, AA, amyloidosis. Rheum Dis Clin North Am 44(4):585–603. https://doi.org/10.1016/j.rdc.2018.06.004

2. Westermark GT, Fändrich M, Westermark P (2015) AA amyloidosis: pathogenesis and targeted therapy. Annu Rev Pathol 10:321–344. https://doi.org/10.1146/annurev-pathol-020712-163913
3. Stojanovic KS, Georgin-Lavialle S, Grateau G (2017) Amylose AA [AA amyloidosis]. Nephrol Ther 13(4):258–264. https://doi.org/10.1016/j.nephro.2017.03.001
4. Okuda Y (2019) AA amyloidosis - benefits and prospects of IL-6 inhibitors. Mod Rheumatol 29(2):268–274. https://doi.org/10.1080/14397595.2018.1515145
5. Okuda Y, Ohnishi M, Matoba K, Jouyama K, Yamada A, Sawada N, Mokuda S, Murata Y, Takasugi K (2014) Comparison of the clinical utility of tocilizumab and anti-TNF therapy in AA amyloidosis complicating rheumatic diseases. Mod Rheumatol 24(1):137–143. https://doi.org/10.3109/14397595.2013.854048
6. Okuda Y, Yamada T, Ueda M, Ando Y (2018) First nationwide survey of 199 patients with Amyloid A amyloidosis in Japan. Intern Med 57(23):3351–3355. https://doi.org/10.2169/internalmedicine.1099-18
7. Gillmore JD, Lovat LB, Persey MR, Pepys MB, Hawkins PN (2001) Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. Lancet 358(9275):24–29. https://doi.org/10.1016/S0140-6736(00)05252-1
8. Wilkins J, Gallimore JR, Tennent GA, Hawkins PN, Limburg PC, van Rijswijk MH, Moore EG, Pepys MB (1994) Rapid automated enzyme immunoassay of serum amyloid A. Clin Chem 40(7 Pt 1):1284–1290
9. Fernández-Nebro A, Olivé A, Castro MC, Varela AH, Riera E, Irigoyen MV, García de Yébenes MJ, García-Vicuña R (2010) Long-term TNF-alpha blockade in patients with amyloid A amyloidosis complicating rheumatic diseases. Am J Med 123(5):454–461. https://doi.org/10.1016/j.amjmed.2009.11.010
10. Lane T, Gillmore JD, Wechalekar AD, Hawkins PN, Lachmann HJ (2015) Therapeutic blockade of interleukin-6 by tocilizumab in the management of AA amyloidosis and chronic inflammatory disorders: a case series and review of the literature. Clin Exp Rheumatol 33(6 Suppl 94):S46–S53
11. Sato H, Sakai T, Sugaya T, Otaki Y, Aoki K, Ishii K, Horizono H, Otani H, Abe A, Yamada N, Ishikawa H, Nakazono K, Murasawa A, Gejyo F (2009) Tocilizumab dramatically ameliorated life-threatening diarrhea due to secondary amyloidosis associated with rheumatoid arthritis. Clin Rheumatol 28(9):1113–1116. https://doi.org/10.1007/s10067-009-1185-0
12. Fukuda M, Sawa N, Hoshino J, Ohashi K, Motoaki M, Ubara Y (2021) Tocilizumab preserves renal function in rheumatoid arthritis with AA amyloidosis and end-stage kidney disease: two case reports. Clin Nephrol 95(1):54–61. https://doi.org/10.5414/CN109971
13. Inoue D, Arima H, Kawanami C, Takiuchi Y, Nagano S, Kimura T, Shimoji S, Mori M, Tabata S, Yanagita S, Matsushita A, Nagai K, Imai Y, Takahashi T (2010) Excellent therapeutic effect of tocilizumab on intestinal amyloid a deposition secondary to active rheumatoid arthritis. Clin Rheumatol 29(10):1195–1197. https://doi.org/10.1007/s10067-010-1422-6
14. Nishida S, Hagihara K, Shima Y, Kawai M, Kuwahara Y, Arimitsu J, Hirano T, Narazaki M, Ogata A, Yoshizaki K, Kawase I, Kishimoto T, Tanaka T (2009) Rapid improvement of AA amyloidosis with humanised anti-interleukin 6 receptor antibody treatment. Ann Rheum Dis 68(7):1235–1236. https://doi.org/10.1136/ard.2008.099267
15. Yamada S, Tsuchimoto A, Kaizu Y, Taniguchi M, Masutani K, Tsukamoto H, Ooboshi H, Tsuruya K, Kitazono T (2014) Tocilizumab-induced remission of nephrotic syndrome accompanied by secondary amyloidosis and glomerulonephritis in a patient with rheumatoid arthritis. CEN Case Rep 3(2):237–243. https://doi.org/10.1007/s13730-014-0127-0
16. Miyagawa I, Nakayamada S, Saito K, Hanami K, Nawata M, Sawamukai N, Nakano K, Yamaoka K, Tanaka Y (2014) Study on the safety and efficacy of tocilizumab, an anti-IL-6 receptor antibody, in patients with rheumatoid arthritis complicated with AA amyloidosis. Mod Rheumatol 24(3):405–409. https://doi.org/10.3109/14397595.2013.844294
17. Jung JY, Kim YB, Kim JW, Suh CH, Kim HA (2021) Biologic therapy for amyloid A amyloidosis secondary to rheumatoid arthritis treated with interleukin 6 therapy: case report and review of literature. Medicine (Baltimore) 100(32):e26843. https://doi.org/10.1097/MD.0000000000026843
18. Kovács A, Cserenyecz A, Baksay B, Kemény É, Szekanecz Z (2020) Successful treatment of rheumatoid arthritis-associated renal AA amyloidosis with tocilizumab. Isr Med Assoc J 22(7):455–457
19. Shimagami H, Katada Y (2019) Successful treatment with tocilizumab for massive ascites due to secondary amyloidosis complicating rheumatoid arthritis: a case report. Scand J Rheumatol 48(6):511–512. https://doi.org/10.1080/03009742.2019.1603325
20. Galmiche S, Buob D, Fellahi S, Bastard JP, Grateau G, Georgin-Lavialle S (2019) Rheumatoid arthritis revealed by polyadenopathy, diarrhea and digestive AA amyloidosis. Joint Bone Spine 86(3):397–398. https://doi.org/10.1016/j.jbspin.2018.07.003
21. Yamagata A, Uchida T, Yamada Y, Nakanishi T, Nagai K, Imakiire T, Oshima N, Kumagai H (2017) Rapid clinical improvement of amyloid A amyloidosis following treatment with tocilizumab despite persisting amyloid deposition: a case report. BMC Nephrol 18(1):377. https://doi.org/10.1186/s12882-017-0799-8
22. Uda H, Saiki O (2017) Tocilizumab postpones the start of hemodialysis compared to conventional oral treatment in amyloid A amyloidosis patients with advanced renal insufficiency by suppressing serum SAA levels. Amyloid 24(1):62–63. https://doi.org/10.1080/13506129.2017.1301420
23. Courties A, Grateau G, Philippe P, Flipo RM, Astudillo L, Aubry-Rozier B, Fabreguet I, Fahd W, Fain O, Guggenbuhl P, Hachulla E, Papo T, Richez C, Sibilia J, Morel J, Berenbaum F, Sellam J (2015) AA amyloidosis treated with tocilizumab: case series and updated literature review. Amyloid 22(2):84–92. https://doi.org/10.3109/13506129.2014.1002031
24. Vinicki JP, De Rosa G, Laborde HA (2013) Renal amyloidosis secondary to rheumatoid arthritis: remission of proteinuria and renal function improvement with tocilizumab. J Clin Rheumatol 19(4):211–213. https://doi.org/10.1097/RHU.0b013e318293793c
25. Hattori Y, Ubara Y, Sumida K, Hiramatsu R, Hasegawa E, Yamanouchi M, Hayami N, Suwabe T, Hoshino J, SawaN OK, Takaichi K (2012) Tocilizumab improves cardiac disease in a hemodialysis patient with AA amyloidosis secondary to rheumatoid arthritis. Amyloid 19(1):37–40. https://doi.org/10.3109/13506129.2011.636460
26. Hakala M, Immonen K, Korpela M, Vasala M, Kauppi MJ (2013) Good medium-term efficacy of tocilizumab in DMARD and anti-TNF-α therapy resistant reactive amyloidosis. Ann Rheum Dis 72(3):464–465. https://doi.org/10.1136/annrheumdis-2012-202156
27. Gupta A, Bagri NK, Tripathy SK, Barwad A, Phulware RH, Hari P (2020) Successful use of tocilizumab in amyloidosis secondary to systemic juvenile idiopathic arthritis. Rheumatol Int 40(1):153–159. https://doi.org/10.1007/s00296-019-04363-z
28. Chantarogh S, Vilaiyuk S, Tim-Aroon T, Worawichawong S (2017) Clinical improvement of renal amyloidosis in a patient with systemic-onset juvenile idiopathic arthritis who received tocilizumab treatment: a case report and literature review. BMC Nephrol 18(1):159. https://doi.org/10.1186/s12882-017-0573-y
29. Okuda Y, Takasugi K (2006) Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. Arthritis Rheum 54(9):2997–3000. https://doi.org/10.1002/art.22118
30. Sharma A, Gupta A, Mitra S, Nada R, Bhattad S, Singh S (2016) Systemic juvenile idiopathic arthritis with amyloidosis: an uncommon complication with a favourable outcome. Indian J Pediatr 83(5):477–478. https://doi.org/10.1007/s12098-015-1913-1
31. Ugurlu S, Hacioglu A, Adibnia Y, Hamuryudan V, Ozdogaz H (2017) Tocilizumab in the treatment of twelve cases with aa amyloidosis secondary to familial mediterranean fever. Orphanet J Rare Dis 12(1):105. https://doi.org/10.1186/s13023-017-0642-0
32. Inui K, Sawa N, Suwabe T, Mizuno H, Yamanouchi M, Hiramatsu R, Hayami N, Hoshino J, Kinowaki K, Fujii T, Ohashi K, Ubara Y (2020) Long term administration of tocilizumab improves renal amyloid A (AA) amyloidosis deposition in Familial Mediterranean fever. Mod Rheumatol Case Rep 4(2):310–311. https://doi.org/10.1080/24725625.2020.1739193
33. Aikawa E, Shimizu T, Koga T, Endo Y, Umeda M, Hori T, Irie J, Kuroda K, Eguchi M, Okamoto M, Tsuji S, Takatani A, Igawa T, Sumiyoshi R, Kawashiri SY, Iwamoto N, Ichinose K, Tamai M, Nakamura H, Origuchi T, Kawakami A (2019) Atypical familial mediterranean fever complicated with gastrointestinal amyloidosis diagnosed due to paroxysmal arthralgia and intractable diarrhea, successfully treated with tocilizumab. Intern Med 58(12):1781–1785. https://doi.org/10.2169/internalmedicine.2277-18
34. Hamanoue S, Suwabe T, Hoshino J, Sumida K, Mise K, Hayami N, Sawa N, Takaichi K, Fujii T, Ohashi K, Yazaki M, Ikeda S, Ubara Y (2016) Successful treatment with humanized anti-interleukin-6 receptor antibody (tocilizumab) in a case of AA amyloidosis complicated by familial

Mediterranean fever. Mod Rheumatol 26(4):610–613. https://doi.org/10.3109/14397595.2014.908810
35. Serelis J, Christaki S, Skopouli FN (2015) Remission of nephrotic syndrome due to AA-amyloidosis, complicating familiar Mediterranean fever, with tocilizumab. Clin Exp Rheumatol 33(6 Suppl 94):S169
36. Yilmaz S, Cinar M, Simsek I, Erdem H, Pay S (2015) Tocilizumab in the treatment of patients with AA amyloidosis secondary to familial Mediterranean fever. Rheumatology (Oxford) 54(3):564–565. https://doi.org/10.1093/rheumatology/keu474
37. Dinoia L, Lopalco G, Cantarini L, Gesualdo L, Rossini M, Iannone F (2017) Long-term tocilizumab efficacy in a patient with psoriatic arthritis and AA amyloidosis. Clin Exp Rheumatol 35(1):170–171
38. Immonen K, Kauppi M, Hakala M (2011) Experiences on the use of biological drugs in psoriatic arthritis-associated amyloidosis. Scand J Rheumatol 40(3):236–238. https://doi.org/10.3109/03009742.2010.530294
39. Eriksson P, Mölne J, Wirestam L, Sjöwall C (2021) Successful treatment of AA amyloidosis in ankylosing spondylitis using tocilizumab: report of two cases and review of the literature. Front Med (Lausanne) 8:661101. https://doi.org/10.3389/fmed.2021.661101
40. Kishida D, Okuda Y, Onishi M, Takebayashi M, Matoba K, Jouyama K, Yamada A, Sawada N, Mokuda S, Takasugi K (2011) Successful tocilizumab treatment in a patient with adult-onset Still's disease complicated by chronic active hepatitis B and amyloid A amyloidosis. Mod Rheumatol 21(2):215–218. https://doi.org/10.1007/s10165-010-0365-8
41 SolísMarquínez MN, GarcíaFernández E, Morís de la Tassa J (2019) Periodic fever: From Still's disease to Muckle-Wells syndrome. Fiebres periódicas: de la enfermedad de Still al síndrome de Muckle-Wells. Reumatol Clin (Engl Ed) 15(5):e39–e40. https://doi.org/10.1016/j.reuma.2017.04.008
42. Saygin C, Uzunaslan D, Hatemi G (2015) Currently used biologic agents in the management of Behcet's syndrome. Curr Med Chem 22(16):1976–1985. https://doi.org/10.2174/0929867322666150209161448
43. Ilbay A, Erden A, Sari A, Armagan B, Aktas BY, Bolek EC, Kalyoncu U, Karadag O (2019) Successful treatment of amyloid A-type amyloidosis due to behçet disease with tocilizumab. J Clin Rheumatol 25(4):43–45. https://doi.org/10.1097/RHU.0000000000000724
44. Redondo-Pachón MD, Enríquez R, Sirvent AE, Andrada E, Noguera-Pons R, Millán I, Amorós F (2013) Tocilizumab treatment for nephrotic syndrome due to amyloidosis in Behcet's disease. Ren Fail 35(4):547–550. https://doi.org/10.3109/0886022X.2013.773913
45. Hočevar A, Lestan B, Šemrl SS, Lakota K, Kojc N, Potočnik N, Tomšič M (2013) AA amyloidosis in a polyarteritis nodosa patient treated with tocilizumab. Amyloid 20(4):275–276. https://doi.org/10.3109/13506129.2013.838947
46. Kos I, Stilgenbauer S, Bewarder M (2020) Renal AA amyloidosis leading to early diagnosis and treatment of takayasu arteritis: a case report and review of the literature. Clin Res Cardiol 109(11):1438–1441. https://doi.org/10.1007/s00392-020-01655-4
47. Ostrovršnik J, Hočevar A, Lestan B, Sodin Šemrl S, Lakota K, Tomšič M (2016) Long-term follow-up on tocilizumab treatment of AA amyloidosis secondary to polyarteritis nodosa. Amyloid 23(4):260–261. https://doi.org/10.1080/13506129.2016.1232648

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