Treatment of secondary Amyloidosis

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INTRODUCTION

- Amyloidosis is a group of diseases characterized by extracellular deposition of betasheet fibrils.
- In the systemic forms, the amyloid causes progressive organ dysfunction, leading to death of the patients.
- Over 30 proteins capable of amyloid formation have been identified.

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NOMENCLATURE ARTICLE

Amyloid nomenclature 2020: update and recommendations by the International Society of Amyloidosis (ISA) nomenclature committee

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ABSTRACT

The ISA Nomenclature Committee met electronically before and directly after the XVII ISA International Symposium on Amyloidosis, which, unfortunately, had to be virtual in September 2020 due to the ongoing COVID-19 pandemic instead of a planned meeting in Tarragona in March. In addition to confirmation of basic nomenclature, several additional concepts were discussed, which are used in scientific amyloid literature. Among such concepts are cytotoxic oligomers, protofibrils, primary and secondary nucleation, seeding and cross-seeding, amyloid signature proteins, and amyloid plaques. Recommendations for their use are given. Definitions of amyloid and amyloidosis are confirmed.

KEYWORDS

Amyloid; fibril protein; nomenclature; aggegation; oligomer; inclusion

Table 1. Amyloid fibril proteins and their precursors in human[a].

Fibril protein	Precursor protein	Systemic and/or localised	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	(Apo) serum amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, lung, ligaments, tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomeninges
Aβ2M	β2-microglobulin, wild type	S	A	Musculoskeletal system
	β2-microglobulin, variants	S	H	ANS
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla and systemic
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney
AGel	Gelsolin, variants	S	H	Kidney PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte chemotactic factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	CNS, PNS, skin
ABri	ABriPP, variants	S	H	CNS
ADan[b]	ADanPP, variants	S	H	CNS
Aβ	Aβ protein precursor, wild type	L	A	CNS
	Aβ protein precursor, variant	L	H	CNS
AαSyn	α-Synuclein	L	A	CNS
ATau	Tau	L	A	CNS
APrP	Prion protein, wild type	L	A	CJD, fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, fatal insomnia
	Prion protein variant	S	H	PNS
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumours
		S	A	Kidney
AIAPP	Islet amyloid polypeptide[c]	L	A	Islets of Langerhans, insulinomas
AANF	Atrial natriuretic factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC[d]	Lung surfactant protein	L	A	Lung
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile aortic, media
AKer	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumours
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic
ACatK[e]	Cathepsin K	L	A	Tumour associated
AEFEMP1[e]	EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1	L	A	Portal veins Aging associated

AA (secondary) amyloidosis

- AA amyloidosis is a disorder characterized by the extracellular tissue deposition of fibrils composed of fragments of serum amyloid A protein (SAA), an acute phase reactant.
- AA amyloidosis may complicate a number of chronic inflammatory conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis, ankylosing spondylitis (AS), inflammatory bowel disease, familial periodic fever syndromes, chronic infections, and certain neoplasms

Chronic inflammatory conditions associated with AA amyloidosis

Chronic inflammatory arthritides	Periodic fevers
Rheumatoid arthritis	Familial Mediterranean fever
Juvenile idiopathic arthritis	Cryopyrin-associated periodic syndrome (CAPS)
Ankylosing spondylitis	TNF receptor-associated periodic syndrome (TRAPS)
Psoriatic arthropathy	Mevalonate kinase deficiency
Reactive arthritis	Deficiency of adenosine deaminase 2 (DADA2)
Adult Still's disease	
Systemic lupus erythematosus	
Gout	
Vasculitides	**Neoplasia**
Polyarteritis nodosa	Hodgkin disease
Takayasu arteritis	Renal cell carcinoma
Behçet syndrome	Adenocarcinoma of the lung, gut, urogenital tract
Giant cell arteritis/polymyalgia rheumatica	Basal cell carcinoma
	Hairy cell leukemia
	Castleman disease
	Hepatic adenoma
	Squamous cell carcinoma
Chronic infections	**Other**
Bronchiectasis	IV and subcutaneous drug misuse
Chronic cutaneous ulcers	Cystic fibrosis
Chronic pyelonephritis	Hidradenitis suppurativa
Chronic osteomyelitis	Kartagener's syndrome
Subacute bacterial endocarditis	Epidermolysis bullosa
Leprosy	Hypogammaglobulinemia
Tuberculosis	Cyclic neutropenia
Whipple's disease	Common variable immunodeficiency
Chronic brucellosis	Hyperimmunoglobulin M syndrome
Inflammatory bowel disease	SAPHO syndrome
Crohn disease	Obesity
Ulcerative colitis	IgG4-related disease
	Sickle cell anemia

TNF: tumor necrosis factor; IV: intravenous; SAPHO: synovitis, acne, pustulosis, hyperostosis, and osteitis; IgG4: immunoglobulin G4.

PROGNOSIS

- If untreated, AA amyloidosis is a serious disease with a significant mortality due to end-stage kidney disease, infection, heart failure, bowel perforation, or gastrointestinal bleeding.

PROGNOSIS

- Patients with persistently high circulating levels of serum amyloid A protein (SAA) are at particular risk of these complications.
- A progressive improvement in survival rates has been reported among patients with AA amyloidosis, likely reflecting, in part, improved treatment strategies for associated inflammatory disorders, as well as earlier detection

ORIGINAL ARTICLE

Natural History and Outcome in Systemic AA Amyloidosis

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ABSTRACT

BACKGROUND

Deposition of amyloid fibrils derived from circulating acute-phase reactant serum amyloid A protein (SAA) causes systemic AA amyloidosis, a serious complication of many chronic inflammatory disorders. Little is known about the natural history of AA amyloidosis or its response to treatment.

METHODS

We evaluated clinical features, organ function, and survival among 374 patients with

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N Engl J Med 2007;356:2361-71

METHODS

We evaluated clinical features, organ function, and survival among 374 patients with AA amyloidosis who were followed for a median of 86 months. The SAA concentration was measured serially, and the amyloid burden was estimated with the use of whole-body serum amyloid P component scintigraphy. Therapy for inflammatory diseases was administered to suppress the production of SAA.

RESULTS

Median survival after diagnosis was 133 months; renal dysfunction was the predominant disease manifestation. Mortality, amyloid burden, and renal prognosis all significantly correlated with the SAA concentration during follow-up. The risk of death was 17.7 times as high among patients with SAA concentrations in the highest eighth, or octile, (≥155 mg per liter) as among those with concentrations in the lowest octile (<4 mg per liter); and the risk of death was four times as high in the next-to-lowest octile (4 to 9 mg per liter). The median SAA concentration during follow-up was 6 mg per liter in patients in whom renal function improved and 28 mg per liter in those in whom it deteriorated ($P<0.001$). Amyloid deposits regressed in 60% of patients who had a median SAA concentration of less than 10 mg per liter, and survival among these patients was superior to survival among those in whom amyloid deposits did not regress ($P=0.04$).

CONCLUSIONS

The effects of renal dysfunction dominate the course of AA amyloidosis, which is associated with a relatively favorable outcome in patients with SAA concentrations that remain in the low-normal range (<4 mg per liter).

and University College Medical School, London.

N Engl J Med 2007;356:2361-71.

PROGNOSIS

- In a review of 374 cases of AA amyloidosis, for example, median survival from diagnosis was 133 months, being of poorer prognostic significance:
- older age,
- reduced serum albumin concentration,
- end-stage renal failure at baseline,
- the degree by which the SAA concentration was elevated during follow-up

TREATMENT OF AA AMYLOIDOSIS

- Control of the underlying disease
- Colchicine
- Dimethylsulfoxide
- Cytotoxic and immunosuppressive agents
- Anticytokine therapy
- Binding to cofactors and peptidic inhibitors
- Clearance of amyloid deposits from tissue
- Investigational approaches

Control of the underlying disease

- The fibril precursor in AA amyloid, SAA, is a normal plasma protein that is produced by hepatocytes as part of the physiologic acute phase response.
- A chronic inflammatory state leads to sustained high levels of the acute phase proteins.

Control of the underlying disease

- Successful treatment of the underlying inflammatory process by, for example, surgical resection of the focus of infection or the tumor, cytotoxic agents and/or biologic agents in rheumatoid arthritis (RA), or antibiotics with chronic infection, results in reduced hepatic production of the acute phase response and a fall in circulating SAA down to normal healthy levels.

Control of the underlying disease

- Over time, this can lead to:
- stabilization of or improvement in renal function,
- reduction in urinary protein excretion,
- partial resolution of amyloid deposits (as assessed in studies by scintigraphy with radiolabeled serum amyloid P component [SAP])

Colchicine

- Colchicine has become accepted prophylactic therapy to prevent AA amyloidosis in FMF, where doses of 0.6 to 1.2 mg/day in adults
- markedly reduced the frequency of attacks of abdominal pain,
- diminished the incidence of clinical renal disease stabilized the glomerular filtration rate in patients with mild proteinuria

Colchicine

- Among FMF patients with nephrotic syndrome due to AA amyloid, prevention of disease progression and a reduction in protein excretion can be achieved.
- a higher colchicine dose of 1.5 to 2.0 mg/day appears to be required, and therapy should be instituted before the plasma creatinine concentration reaches 1.5 mg/dL.

Colchicine

- Colchicine is not likely to be effective in salvaging renal function in FMF patients who already have chronic renal failure, since irreversible glomerular injury is probably present.
- However, it can prevent recurrent disease in the transplant and prevent progressive amyloid deposition in other sites

Colchicine

- Anecdotal successes with chronic colchicine therapy (0.6 mg twice daily) have also been reported in patients with AA amyloid due to
- inflammatory bowel disease,
- Behçet syndrome,
- intravenous drug users with suppurative skin lesions. Proteinuria due to renal amyloidosis may be markedly reduced, and renal function may remain stable over long periods of time

Dimethylsulfoxide

- Dimethylsulfoxide (DMSO) may have anti-amyloid activity in several forms of the disorder;
- It has been shown to be active in murine models of AA amyloidosis and in case reports of patients with AA amyloid due to rheumatoid arthritis or to Crohn disease.

Dimethylsulfoxide

- Use of DMSO is limited, however, by its acrid odor and, because of its potent solvent activity, by the difficulty attaining purity for pharmaceutical usage

Cytotoxic and immunosuppressive agents

- Azathioprine, chlorambucil, methotrexate, and cyclophosphamide have been shown to be helpful in AA amyloidosis complicating treatment-responsive inflammatory diseases in individual case reports and small series.

Rheumatology 2001;40:821–825

Renal type AA amyloidosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide

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Abstract

Objective. To determine the incidence of renal AA amyloidosis and its association with rheumatoid arthritis (RA) in a cohort of all renal biopsies at one referral hospital and to measure the effect of a monthly pulse of cyclophosphamide on renal function and survival in these RA patients.

Objective. To determine the incidence of renal AA amyloidosis and its association with rheumatoid arthritis (RA) in a cohort of all renal biopsies at one referral hospital and to measure the effect of a monthly pulse of cyclophosphamide on renal function and survival in these RA patients.

Method. All renal biopsies with proven AA amyloidosis from a single pathology unit linked to a major nephrology referral unit in a university hospital were selected retrospectively and RA patients were identified. We studied 6931 renal biopsies. The effect of treatment with and without pulse cyclophosphamide on renal function and survival was studied in these patients.

Results. From March 1977 to February 1990, the incidence of AA amyloidosis was 2.4 cases/yr. The incidence and prevalence of the association of AA amyloidosis with RA were 0.68 cases/yr and 0.22% (15/6931) respectively. RA patients treated with cyclophosphamide ($n = 6$) had a lower rate of renal function loss ($P = 0.013$) and a higher median survival ($P = 0.026$) than untreated patients ($n = 9$). During the follow-up period, two out of six treated patients (33%) and all nine untreated patients (100%) died.

Conclusions. AA amyloidosis is a rare complication of RA and complicates the evaluation of treatment. This retrospective study suggests that treatment with cyclophosphamide is able to reduce the incidence of end-stage renal failure and to increase survival. Prospective studies are needed to clarify this issue.

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Efficacy of cyclophosphamide combined with prednisolone in patients with AA amyloidosis secondary to rheumatoid arthritis

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•Satoshi Baba

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Abstract

Secondary amyloid A (AA) amyloidosis is an uncommon yet important complication of rheumatoid arthritis (RA). It is one of the most relentless of the extra-articular features of RA, and suitable treatments have not yet been found. We studied the efficacy of cyclophosphamide (CYC) combined with prednisolone (PSL) in amyloidotic patients who had serum amyloid A (SAA) 1.3 genotype, which is a risk factor for secondary amyloidosis in Japanese RA patients. Fifteen RA patients who were SAA1.3 homo- and heterozygotes with biopsy-confirmed AA amyloidosis were treated with a combination of CYC and PSL. Laboratory variables of C-reactive protein (CRP), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), serum albumin (Alb), serum creatinine (Cre) and Lansbury's index were carried out by statistical analysis of changes between before and during the medication. According to the Mann–Whitney rank test, CRP, RF, ESR, Alb and Cre levels improved significantly with the combination treatment ($p<0.05$). Also, paired *t*-tests showed significance in Lansbury's index between before and during the medication ($p=0.007$). CYC combined with PSL ameliorated not only laboratory markers but also clinical rheumatoid activity in patients with amyloidosis secondary to RA, whose genotypes were SAA1.3 homo- and heterozygous. CRP, ESR, RF, Alb and Cre will be surrogate markers of therapeutic efficacy. The combination of CYC and PSL appears to be beneficial for Japanese RA patients who are SAA1.3 homo- and heterozygous carriers, associated with secondary AA

Anticytokine therapy

- Increasing use of biologics with activities against proinflammatory cytokines (TNF-alpha, IL-1, and IL-6) for diseases such as RA, psoriatic arthritis, and ankylosing spondylitis (AS) may reduce the risk of development of AA amyloid **as well as treating existing amyloidosis.**

Anticytokine therapy

- The majority of published experience that has shown efficacy has involved patients with RA and has reported on the first-generation TNF-alpha antagonists (ie, etanercept, infliximab, and adalimumab).
- In one large study involving 86 patients with RA complicated by AA amyloidosis, etanercept was superior to cyclophosphamide independent of the SAA 1.3 allele

Comparative Study

•. 2012 Nov;51(11):2064-9.

doi: 10.1093/rheumatology/kes190. Epub 2012 Aug 9.

Effectiveness of etanercept vs cyclophosphamide as treatment for patients with amyloid A amyloidosis secondary to rheumatoid arthritis

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•PMID: 22879465

•DOI: 10.1093/rheumatology/kes190

Abstract

Objectives: To compare the effectiveness of an alkylating agent with that of a biologic agent in the treatment of patients with amyloid A (AA) amyloidosis secondary to RA and to assess the association of the serum AA (SAA) 1.3 allele with treatment.

Methods: CYC and etanercept (ETN) were administered to 62 and 24 RA patients, respectively, who were confirmed with biopsy as having AA amyloidosis. We evaluated whether the SAA1.3 allele, a factor indicating genetic risk and poor prognosis of Japanese RA patients with AA amyloidosis, influenced treatments and retrospectively analysed the effectiveness of both agents via statistical methods.

Results: Two treatment groups were similar, except for the SAA1.3 genotype ($P = 0.015$) and duration of AA amyloidosis since diagnosis ($P < 0.001$). Also, patients given ETN had somewhat worse renal function, i.e. 24-h proteinuria ($P = 0.02$), at the initiation of treatment. ETN demonstrated greater effectiveness than CYC, as shown by significantly improved levels of serum CRP and serum albumin (both $P < 0.01$) and estimated glomerular filtration rate (eGFR; $P = 0.032$). ETN improved survival ($P = 0.025$), and the hazard ratios for the risk of death endpoint with eGFR and 24-h proteinuria were significant by $P = 0.024$ and $P = 0.025$, respectively. The SAA1.3 allele did not affect the response to medications in AA amyloidosis secondary to RA.

Conclusion: ETN treatment was more effective than CYC treatment, and CRP, albumin and eGFR may be valuable biomarkers for analysis. The SAA1.3 allele was not a factor affecting treatment in Japanese patients with AA amyloidosis secondary to RA.

Anticytokine therapy

- The effectiveness of the TNF antagonists appears to be directly related to their ability to control the underlying inflammatory disorder and may be enhanced by pulse therapy with glucocorticoids for induction.

Anticytokine therapy

- This experience has been extended to AA amyloidosis complicating AS and Crohn disease, with regression of tissue amyloid occurring as early as three months, documented by gastrointestinal biopsies in some instances.

Anticytokine therapy

- Efficacy of biologic response modifiers (BRMs) may be responsible in part for the marked decline in the incidence of renal replacement therapy for amyloidosis associated with inflammatory rheumatic diseases reported to nationwide registries in Finland during the period 1999 to 2008

Anticytokine therapy

- Efficacy of the rapidly acting IL-1 receptor antagonist (IL-1ra) anakinra has been established for the 20 to 30 percent of cases of "idiopathic" AA amyloidosis reported in large series.

•. 2017 Sep;24(3):189-193.
doi: 10.1080/13506129.2017.1352503. Epub 2017 Jul 26.

Safety and efficacy of empirical interleukin-1 inhibition using anakinra in AA amyloidosis of uncertain aetiology

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•PMID: 28745926
•DOI: 10.1080/13506129.2017.1352503

Abstract

Objective: AA amyloidosis is a serious complication of persistent inflammation, which, untreated will progress to renal failure and death. Effective suppression of the underlying inflammatory disease is the focus of treatment. However, in approximately 20% of cases the underlying condition remains uncertain, presenting a dilemma as to choice of treatment.

Methods: We conducted a retrospective study of a cohort of 11 patients diagnosed with AA amyloidosis of unknown aetiology, who had been empirically treated with anakinra.

Results: In anakinra-responders, median pre-treatment SAA was 74 (IQR 34-190) mg/L, and median on-treatment SAA was 6 (4-16) mg/L ($p = .0047$), with the response having been maintained for a median on-treatment follow-up of 1.8 (1-7.6) years. Six dialysis patients were treated effectively and safely with 100 mg anakinra three times weekly post-dialysis. Four patients remained well on daily anakinra post-renal transplant. Five anakinra-responders showed regression and three showed stabilization of amyloid load on serial SAP scintigraphy.

Conclusions: This small cohort shows that even in potentially high risk cases with organ damage secondary to AA amyloidosis or in the presence of a renal graft, anakinra, when used appropriately and carefully monitored, has proved remarkably effective and well tolerated. Longer follow-up of this off-label use is required.

Anticytokine therapy

- Since 2006, with the first report of the effectiveness of a humanized anti-IL-6 receptor antibody (tocilizumab) for the treatment of AA amyloidosis complicating juvenile chronic polyarthritis, there has been a large experience with the use of this biologic agent to improve AA amyloid complicating adult RA, as well as isolated case reports in patients with Behçet syndrome, polyarteritis nodosa, Castleman disease, autoinflammatory disease, and Crohn disease.

Anticytokine therapy

- Tocilizumab has been used effectively in patients with RA and renal insufficiency due to AA amyloid, with biologic activity manifesting as a dramatic and rapid drop in C-reactive protein (CRP) and SAA levels to normal compared with more traditional treatments, such as methotrexate or TNF-alpha antagonists, with a significantly lower incidence of progression to hemodialysis over time.

Anticytokine therapy

- In a retrospective review of 42 patients with RA and AA amyloidosis treated with tocilizumab or TNF antagonists, the former was more efficient in normalizing SAA levels, and was a more effective strategy for treating AA amyloidosis.
- By contrast, although TNF inhibitors may reduce SAA levels in clinical practice, complete normalization is rare

frontiers in Medicine

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Successful Treatment of AA Amyloidosis in Ankylosing Spondylitis Using Tocilizumab: Report of Two Cases and Review of the Literature

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Anticytokine therapy

- Anticytokine therapy remains an option for patients presenting with renal insufficiency who undergo renal transplantation as prophylaxis to prevent recurrence of AA amyloid in the allograft; in particular, IL-1 inhibitors may be especially beneficial in this setting.
- In addition, the calcineurin inhibitor FK506 (tacrolimus), which is commonly used to prevent allograft rejection, may also slow progression of AA amyloid, based on animal studies.

Anticytokine therapy

- Demonstration of the efficacy of available anticytokines holds the promise that novel monoclonal antibodies and low molecular weight (mw) inhibitors in phase 2/3 trials may also prove useful for the inhibition of the deposition phase of SAA amyloid.
- In particular, tofacitinib, which is approved for the treatment of RA, has potential for the inhibition of both IL-6 and SAA in AA amyloidosis

Binding to cofactors and peptidic inhibitors

- New classes of agents may eventually prove efficacious by interfering with fibril formation.
- Low mw anionic sulfonates or sulfates, as well as low mw heparins, impede AA fibril formation in vitro and attenuate the development of murine AA amyloid.

Binding to cofactors and peptidic inhibitors

- This hypothesis was tested in a randomized, multicenter international phase II/III trial of the first of these compounds (eprodisate) for the treatment of 150 patients with AA amyloid.

Binding to cofactors and peptidic inhibitors

- In this study, eprodisate showed a clinical benefit in delaying the decline in renal function for AA amyloidosis patients, defined as a reduction in risk and delayed time to doubling of serum creatinine, to 50 percent decrease in creatinine clearance, or to progression to dialysis, end-stage kidney disease, or death (from all causes).

Binding to cofactors and peptidic inhibitors

- Unfortunately, a second international phase 3 randomized trial (ClinicalTrials.gov identifier: NCT012157470) failed to confirm benefit, and drug development has been terminated.
- An alternative strategy is the design of low mw peptides complementary to SAA domains critical for self-aggregation in order to inhibit fibrillogenesis.

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DOI 10.1007/s00726-015-2167-y

ORIGINAL ARTICLE

Designing peptidic inhibitors of serum amyloid A aggregation process

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Abstract Amyloid A amyloidosis is a life-threatening complication of a wide range of chronic inflammatory, infectious and neoplastic diseases, and the most common form of systemic amyloidosis worldwide. It is characterized by extracellular tissue deposition of fibrils that are composed of fragments of serum amyloid A protein (SAA), a major acute-phase reactant protein, produced predominantly by hepatocytes. Currently, there are no approved therapeutic agents directed against the formation of fibrillar SAA assemblies. We attempted to develop peptidic inhibitors based on their similarity and complementarity to the regions critical for SAA self-association, which they should interact with and block their assembly into amyloid fibrils. Inh1 and inh4 which are comprised of the residues from the amyloidogenic region of SAA1.1 protein and Aβ peptide, respectively, were found by us as capable to significantly suppress aggregation of the SAA1-12 peptide. It was chosen as an aggregation model that mimicks the amyloidogenic nucleus of SAA protein. We suppose that aromatic interactions may be responsible for inhibitory activity of both compounds. We also recognized that aromatic residues are involved in self-association of SAA1-12.

Clearance of amyloid deposits from tissue

- A novel bis (proline) compound (CPHPC) has been developed that binds with high affinity to serum amyloid P component (SAP), binding to amyloid fibrils, resulting in rapid clearance of SAP by the liver and depleting its serum level by approximately 90 percent.
- In a preliminary report, this resulted in disappearance of deposits in three types of systemic amyloidosis (AL, ATTR, and AA), as assessed by SAP scintigraphy.

•. 2002 May 16;417(6886):254-9.
doi: 10.1038/417254a.

Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis

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Abstract

The normal plasma protein serum amyloid P component (SAP) binds to fibrils in all types of amyloid deposits, and contributes to the pathogenesis of amyloidosis. In order to intervene in this process we have developed a drug, R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid, that is a competitive inhibitor of SAP binding to amyloid fibrils. This palindromic compound also crosslinks and dimerizes SAP molecules, leading to their very rapid clearance by the liver, and thus produces a marked depletion of circulating human SAP. This mechanism of drug action potently removes SAP from human amyloid deposits in the tissues and may provide a new therapeutic approach to both systemic amyloidosis and diseases associated with local amyloid, including Alzheimer's disease and type 2 diabetes.

Clearance of amyloid deposits from tissue

- Administration of a humanized monoclonal anti-SAP antibody following CPHPC treatment has been shown to trigger clearance of amyloid deposits from the liver, kidney, and other tissues in an early phase trial in patients with systemic amyloidosis, including a patient with AA amyloidosis, as well as patients with AL and hereditary forms of amyloidosis.
- This effect has subsequently been updated to include patients with cardiac amyloidosis preparatory to a phase 3 multicenter trial.

Repeat doses of antibody to serum amyloid P component clear amyloid deposits in patients with systemic amyloidosis

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Systemic amyloidosis is a fatal disorder caused by pathological extracellular deposits of amyloid fibrils that are always coated with the normal plasma protein, serum amyloid P component (SAP). The small-molecule drug, miridesap, [(R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC)] depletes circulating SAP but leaves some SAP in amyloid deposits. This residual SAP is a specific target for dezamizumab, a fully humanized monoclonal IgG1 anti-SAP antibody that triggers immunotherapeutic clearance of amyloid. We report the safety, pharmacokinetics, and dose-response effects of up to three cycles of miridesap followed by dezamizumab in 23 adult subjects with systemic amyloidosis (ClinicalTrials.gov identifier: NCT01777243). Amyloid load was measured scintigraphically by amyloid-specific radioligand binding of ^{123}I-labeled SAP or of ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid. Organ extracellular volume was measured by equilibrium magnetic resonance imaging and liver stiffness by transient elastography. The treatment was well tolerated with the main adverse event being self-limiting early onset rashes after higher antibody doses related to whole body amyloid load. Progressive dose-related clearance of hepatic amyloid was associated with improved liver function tests. ^{123}I-SAP scintigraphy confirmed amyloid removal from the spleen and kidneys. No adverse cardiac events attributable to the intervention occurred in the six subjects with cardiac amyloidosis. Amyloid load reduction by miridesap treatment followed by dezamizumab has the potential to improve management and outcome in systemic amyloidosis.

Investigational approaches

- Design of or search for ligands that stabilize the native conformation of subunit proteins
- Capping and stabilization of prefibrillar aggregates
- Ligands or monoclonal antibodies specific for lipid-free SAA oligomers
- Development of drugs that inhibit the adoption of the beta-pleated sheet configuration (either generically or specifically to the type of amyloid)
- Use of chaperones to reverse aggregation
- Alterations of the milieu that is responsible for off-pathway aggregation
- Development of other methods to stimulate resorption of amyloid from tissue


THANK YOU