

# Recent advances in the treatment of familial amyloid polyneuropathy

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**Abstract:** The treatment of familial amyloid polyneuropathy (FAP) requires a multidisciplinary approach, mainly neurological and cardiological. It includes specific treatments to stop the progression of systemic amyloidogenesis, the symptomatic treatment of the peripheral and autonomic neuropathy and the treatment of organs severely involved by amyloidosis (heart, eyes, kidneys). First-line specific treatment of met30 transthyretin (TTR) FAP is liver transplantation, which allows suppression of the main source of mutant TTR, to stop the progression of the neuropathy in 70% of cases in the long term and to double the median survival. In cases of severe renal or cardiac insufficiency, a combined kidney–liver or heart–liver transplantation can be discussed. Tafamidis (Vyndaqel) is a novel specific stabilizer of TTR which, in the very early stages of met30 TTR FAP, slows the progress of peripheral neuropathy. This drug should be proposed in cases of stage 1 symptomatic polyneuropathy. Other innovative medicines have been developed by biopharmaceutical companies to block the hepatic production of mutant and wild type TTR which are harmful in late-onset FAP (> 50 years old), including RNA interference therapeutics and antisense oligonucleotides, and to remove the amyloid deposits (monoclonal antibody antiserum amyloid P). Clinical trials should first assess patients with late onset FAP or non-met30 TTR FAP who are less responsive to liver transplantation or in case of significant progression of the neuropathy with Vyndaqel. Initial cardiac assessment and periodic cardiac investigations are important for patients with FAP because of the frequency of cardiac impairment, which is responsible for the high rate of mortality. Prophylactic pacemaker treatment should be discussed. Symptomatic treatments are required to improve patients' quality of life. Familial screening of people with TTR mutation and regular follow up are essential. Appropriate clinical examination and complementary investigations are vital for the early detection of disease onset and to start specific therapy as soon as possible.

**Keywords:** familial amyloidosis with polyneuropathy, gene therapy, liver transplantation, tafamidis, treatment

## Introduction

Familial amyloid polyneuropathy (FAP) is a progressive, disabling and life-threatening polyneuropathy affecting the peripheral and autonomic nervous system. FAP is an autosomal transmission disorder which is usually due to a point mutation of the transthyretin (TTR) gene [Benson and Kincaid, 2007]. The natural history of the disease was described 30 years ago in patients of Portuguese origin with early onset (<50 years) [Coutinho *et al.* 1980] and more recently in patients with late onset in Japan ( $\geq$ 50 years) [Koike *et al.* 2012] (Table 1). Study and

follow up of a cohort of 483 Portuguese patients with FAP in Porto enabled the disease course to be described in three stages [Coutinho *et al.* 1980]. Another staging system concerned the progression of walking disability in FAP [Steen and Ek, 1983] (Table 2). The course of late onset met30 TTR FAP has recently shown major functional severity, faster progression of sensorimotor polyneuropathy and reduced survival [Koike *et al.* 2012].

FAP is a multivisceral and life-threatening disease resulting in multiple disabilities for which a

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**Table 1.** Particularities of early and late onset familial amyloid polyneuropathy and its course.

	Early onset met30 TTR FAP [Coutinho <i>et al.</i> 1980; Koike <i>et al.</i> 2002]	Late onset met30 TTR FAP [Koike <i>et al.</i> 2002 ; Koike <i>et al.</i> 2012]
Age of onset	<50 years	>50 years
Country	Portugal, Japan, Brazil	Sweden, France, UK, Italy, Japan
Positive family history	94%	48%
Initial clinical presentation		
Peripheral neuropathy	57%	81%
Autonomic neuropathy	48%	10%
Weight loss	5%	0
Mean delay for aid for walking	>5.6 years	3 years
Cardiac	Progressive conduction disorders	Restrictive cardiomyopathy Cardiac insufficiency
Median survival	11 years	7.3 years
Causes of death	Cachexia, infections	Cardiac insufficiency Sudden death Cachexia or secondary infection

FAP, familial amyloid polyneuropathy; TTR, transthyretin.

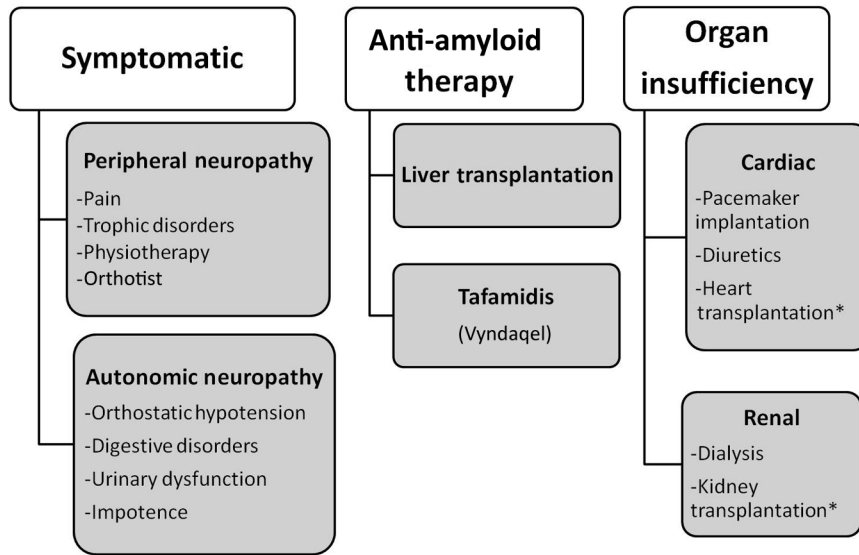
**Table 2.** Stages of familial amyloid polyneuropathy for locomotion.

Coutinho <i>et al.</i> [1980]	Duration of stage	Yamamoto <i>et al.</i> [2007]
Stage 1 The disease is limited to the lower limbs Walking without any help. Slight weakness of the extensors of the big toes.	5.6 ± 2.8 years	PND I Sensory disturbances in extremities Preserved walking capacity
Stage 2 Motor signs progress in lower limbs with steppage and distal amyotrophies, the muscles of the hands begin to be wasted and weak. The patient is by then obviously handicapped but can still move around, although needing help.	4.8 ± 3.6 years	PND II Difficulties walking but without the need for a walking stick
		PND IIIa One stick or one crutch required for walking.
		PND IIIb Two sticks or two crutches required for walking
Stage 3 The patient is bedridden or confined to a wheelchair, generalized weakness and areflexia.	2.3 ± 3.1 years	PND IV Patient confined to a wheelchair or a bed

PND, a modified polyneuropathy disability score.

national referral center was set up in France in 2005 [Adams *et al.* 2012b]. Therapy for FAP is complex and requires a multidisciplinary approach: first, specific therapy to prevent production of amyloids; second, symptomatic therapy of

sensorimotor and autonomic polyneuropathy, and cardiac and renal injury; finally, treatment of end-stage cardiac or renal failure (Figure 1). During the past 20 years treatment of FAP has benefited from advances in drugs that have



**Figure 1.** Principles of therapy for familial amyloid polyneuropathy.  
\*: in association with liver transplantation.

enabled management of the disease and modification of its natural history.

### Symptomatic treatments

Symptomatic treatments are important in patients with FAP to improve their quality of life. These include treatment of manifestations of sensorimotor polyneuropathy, prevention and cure of trophic disorders, physiotherapy, help of an orthesist (Orthotist), control of autonomic dysfunction (digestive – diarrhea, gastroparesis; urinary and genital dysfunction; orthostatic hypotension), treatment of associated ophthalmologic manifestations (glaucoma, vitreous opacities) and cardiac disorders.

### Treatment of organ complications

#### Cardiac involvement

Treatment of cardiac complications depends on the type and the severity of the cardiopathy. Assessment of the cardiac function must be systematic in patients with FAP as it is usually sub-clinical and requires a cardiac checkup. Conduction disorders, which are common and evolutive, must be tested using an electrocardiogram (ECG), Holter recording and an intracardiac ECG if necessary [Eriksson *et al.* 1984]. Detection of severe conduction disorders often requires prophylactic pacemaker implantation [Eriksson and Olofsson, 1984]. Evaluation of cardiac function and impact

of myocardial amyloid infiltration on ventricular function is extremely important. Severe cardiac injury may constitute a contraindication for liver transplantation (LT), while a combined heart and liver transplantation can be considered.

In severe renal injury due to amyloidosis, hemodialysis and later a renal transplantation may be required.

### Anti-amyloid therapy

It is important to search systematically for familial amyloidosis in cases of suspected amyloid light-chain amyloidosis because anti-amyloid therapy differs radically and requires chemotherapy.

### Twenty years' experience of liver transplantation

LT was proposed 20 years ago to suppress the main source of mutant TTR, which is amyloidogenic, to prevent formation of amyloidosis and to stop progression of the disease [Holmgren *et al.* 1991, 1993]. More than 2000 patients with FAP underwent LT worldwide [Wilczek *et al.* 2011], half of them in Portugal and 200 in France. The results of the LT depend on the TTR gene mutation, the age of the patient and the stage of the disease.

The initial results concerned the biological effect, with 98% reduction of mutated TTR in the days following LT [Adams *et al.* 2000; Holmgren *et al.*

1991]. Afterwards, the effects of LT on neuropathy were evident since its progression was stopped in 70% of patients at mid term. This has been established for met30 TTR FAP according to the following objective parameters: clinical, functional, neurophysiological and histopathological, with a major reduction in axon loss [Adams *et al.* 2000]. These findings were confirmed in the long term. LT does not allow either clinical or functional recovery [Adams *et al.* 2000; Yamamoto *et al.* 2007]; autonomic dysfunctions are unchanged.

Worsening of walking ability is possible after LT, seen in one-third of our cohort of patients after LT (personal data). Twenty percent required an aid for walking after LT (median delay of 11 years) (unpublished data). Independent risk factors for requiring aid for walking were major weight loss, previous walking difficulties and a late onset at LT. Worsening of walking ability may be explained by accumulation of wild type TTR in the nerve after LT [Liepnieks *et al.* 2010]. For non-met30 TTR FAP, success of LT is less common. The benefit of LT on neuropathy is better when LT is performed at an early stage, before the onset of walking difficulties that require aid.

#### *Effects on survival*

Although LT doubles the median survival in early onset met30 TTR FAP, the impact of LT on survival for non-met30 TTR FAP is less obvious. The rate of survival at 5 years for patients with FAP after LT is 82% in met30 TTR FAP *versus* 59% in non-met30 TTR FAP according to the world register of LT in FAP [Wilczek *et al.* 2011]. Independent risk factors of mortality in our center are severe autonomic dysfunction, late onset and non-met30 TTR mutation (unpublished data). Long-term follow up of early onset met30 TTR FAP shows a rate of survival of 100% in patients after LT *versus* 56.1% in those who did not have a transplant after 10 years [Yamashita *et al.* 2012].

#### *Effects on organ and ocular involvement*

The effects of LT on cardiac involvement depend on the type of initial cardiopathy and the genotype, early or late onset, or TTR variant (met30 or non-met30). Progress of cardiopathy is possible after LT, marked by the following:

- (1) Progressive thickening of the myocardium on echocardiogram after LT in late onset met30 TTR FAP in Sweden,

explaining the possible development of congestive heart failure after LT [Olofsson *et al.* 2002].

- (2) Development of conduction disorders requiring pacemaker implantation in 8% [Yamamoto *et al.* 2007] to 20% of cases after LT (personal communication, unpublished data).

Worsening of cardiopathy after LT can be explained by accumulation of wild type TTR in the myocardium [Yazaki *et al.* 2000]. Periodic assessment of patients after LT is necessary due to the ongoing risk of progress of cardiopathy after LT, both on conduction disorders and restrictive cardiomyopathy.

Renal function is stable in most patients after LT, but cases of deterioration during the first quarter after LT requiring hemodialysis have been reported [Rocha *et al.* 2011]. Chronic renal failure (34%), including 5% terminal end-stage disease after LT, is also possible [Ferreira *et al.* 2012].

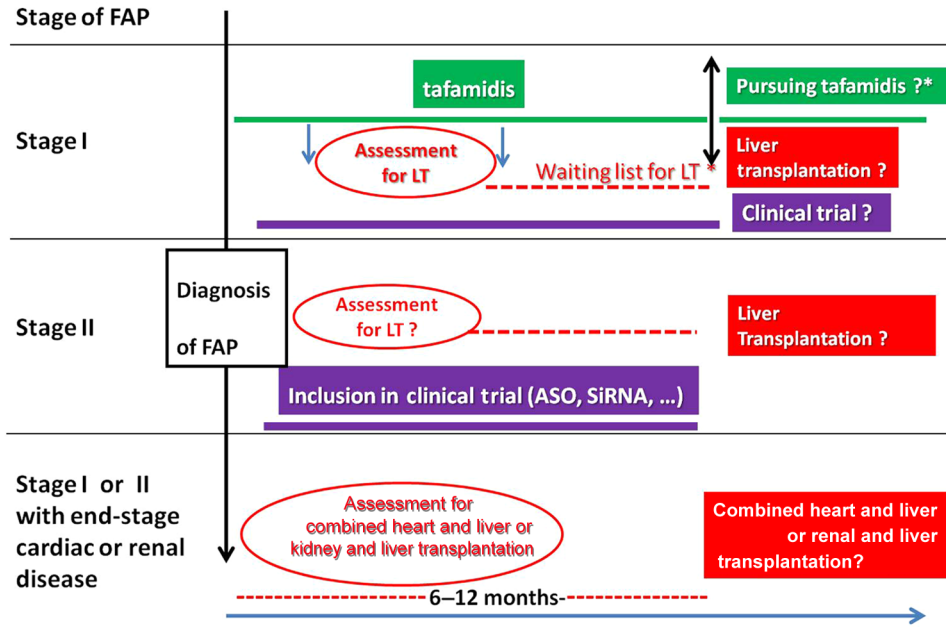
Combined heart and liver transplantation [Raichlin *et al.* 2011] and kidney and liver transplantation must be discussed in cases of severe life-threatening cardiomyopathy or end-stage renal disease requiring dialysis.

Ocular manifestations are not influenced by LT, with a persisting risk of developing glaucoma or vitreous opacities in 8% and 12%, respectively due to the retinal source of mutated TTR [Sandgren *et al.* 2008].

#### *Morbidity and mortality*

In our series of 200 patients who have had LT since 1993, 38% died, including 14% in the first year until 15 years after LT. Mortality during the first year is higher in patients with non-met30 TTR FAP *versus* met30 TTR FAP. Deaths during the first year are due to cardiac causes (sudden death, cardiac insufficiency), infections or hepatic failure, as a direct result of surgery in 3.5% [Yamamoto *et al.* 2007]. After the first year, patients died from progress of the amyloid disease (50%), affecting the heart or peripheral nervous system, or varied causes, including infection, stroke, suicide, hepatic causes.

Delay for LT varies from 6 to 12 months according to the rules fixed by the National Biomedical Agency. The waiting list for LT may vary from



**Figure 2.** Therapeutic strategy in patients with familial amyloid polyneuropathy (FAP) according to the stage of the disease [Coutinho *et al.* 1980]. Stage III (wheelchair bound or bedridden) is a contraindication for any transplantation, liver alone or combined liver plus kidney and liver plus heart. ASO, antisense oligonucleotide; LT, liver transplantation; siRNA small interfering RNA.

6 to 18 months due to the shortage of donor organs (cadaveric donor) and a need to match donor and patient blood and body type. A patient with a very common blood type has less chance of quickly finding a suitable liver. Avoiding a long wait is possible if a patient has a living donor who is willing to donate part of their liver (living donor transplantation) via a partial hepatic graft. In such cases, the delay may be as short as 4 months. If the donor is a family member, they must not carry the TTR gene mutation.

*Side effects of liver transplantation*

LT is associated with the risks of surgery and acute liver rejection, which is usually controlled by pulses of methylprednisolone or modification of immunosuppressive drugs. LT is associated with an increased risk of infections, mainly during the first year after surgery, including septicemia which are usually favored by urinary incontinence [Adams *et al.* 2000; Yamamoto *et al.* 2007], and pulmonary infections which may be opportunistic in half of the cases (pneumocystosis, cytomegalovirus). Patients may develop acute renal failure (26%) after orthotopic LT [Ferreira *et al.* 2012] or chronic renal failure (34%) which may lead to end-stage renal disease (5.1%). The risk of

chronic renal insufficiency is associated with renal insufficiency before LT and onset of acute renal failure after LT (Ferreira *et al.* 2012). pre-OLT is an independent risk factor [Ferreira *et al.* 2012; Lobato and Rocha, 2012]. Orthotopic LT may also be associated with cancer or lymphoproliferative syndrome (1% of cases) both favored by immunosuppressive drugs.

*Immunosuppressants to use and their long-term risk/benefit ratio*

The immunosuppressants we usually use are calcineurin inhibitors (CNI): ciclosporin or tacrolimus. The risk of acute rejection is about 20% with a loss of graft by chronic rejection below 5%. Liver transplant recipients are at high risk of developing acute and chronic renal failure as a consequence of the use of CNI. These two drugs have also a similar toxicity profile, which may compromise the long term benefits of liver transplantation (LT) and the quality of life after liver transplantation: at 10-year-post LT, the rate of chronic renal failure, arterial hypertension, and diabetes is 30%, 40% and 10-20% of cases, respectively. In addition, there is an overall increase of cardiovascular complications and of *de novo* tumors. Frequently, mycophenolate mofetil, a

**Table 3.** State of progress of clinical trials with anti-amyloid drugs.

Treatment	Preclinical experimental	Administration	Phase I	Phase II	Phase III	Marketing authorization
Tafamidis*	–	Oral		2007	–>2009	EMA : November 2011 ANSM: September 2011 FDA: No
Diflunisal <sup>§</sup>	–	Oral			–>2010	
DOXY-TUDCA <sup>‡</sup>	+	Oral		Current		
ASOs <sup>§</sup>	+	SCI	Current		2013	
SiRNA <sup>¶</sup>	+	IVI	2011–2012	2012	2013?	
Anti-SAP Mab <sup>#</sup>	+	IVI	2013?			

\*Coelho *et al.* [2012]; <sup>§</sup>Berk *et al.* [2011]; <sup>‡</sup>Cardoso *et al.* [2010], Obici *et al.* [2012]; <sup>§</sup>Ackermann *et al.* [2012], Benson *et al.* [2006]; <sup>¶</sup>Coelho *et al.* [2011]; <sup>#</sup>Bodin *et al.* [2010].

ANSM, Agence nationale de sécurité du médicament et des produits de santé; ASO, antisense oligonucleotide; DOXY-TUDCA, doxycycline taurodesoxycholic acid; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IVI, intravenous infusion; SCI, subcutaneous injection.

non-nephrotoxic immunosuppressor, is added to CNI to avoid overdose of CNI and to preserve post-transplant renal function.

#### Timing of surgery

We must take into account the waiting list which varies between 6 and 18 months; during this time the disease may worsen (Figure 2). As LT is able to stop progress of the disease, LT should be performed as soon as possible, early in the course of the disease [Yamashita *et al.* 2012].

#### Domino liver transplantation

To compensate for the lack of donors for LT, it is proposed that livers from patients with FAP which are normal except for production of the mutant TTR are used as a graft for patients with severe liver diseases. This is called domino LT (DLT). These patients are at risk of developing acquired amyloid neuropathy [Adams *et al.* 2011; Stangou *et al.* 2005] that may justify retransplantation. In a prospective study to assess the risk–benefit ratio of DLT, systemic amyloidosis developed early with amyloid deposits on labial salivary gland biopsy (LSGB) 5 years after DLT in half of patients [Adams *et al.* 2011] or on rectal biopsy in one-third of patients [Llado *et al.* 2010]. In DLT recipients, nerve biopsy is crucial [Adams *et al.* 2011] to prove that the neuropathy is due to amyloidosis and not other causes [Adams *et al.* 2011; Llado *et al.* 2010]. The delay to declare polyneuropathy ranges from 3.5 [Adams *et al.* 2011] to 9 years [Conceicao *et al.* 2010]. *De novo* amyloid neuropathy mimics FAP of early onset [Adams *et al.* 2011].

#### Anti-amyloid medicine

During the past 5 years, several therapeutic strategies for FAP have been developed as an alternative to LT. This has allowed the first anti-amyloid medicine to benefit from a marketing authorization in Europe and France but not in the USA. Multicentric clinical trials for other medicines for FAP should start soon (Table 3).

#### Kinetic stabilizer of transthyretin

The mechanism of action of this class of medicine is stabilization of mutant TTR by binding to the T4 binding sites and stabilizing the TTR tetramer, allowing prevention of dissociation in monomers and amyloidogenic and toxic intermediaries [Johnson *et al.* 2012]. Efficiency of this treatment has been shown *in vitro* in the serum of treated patients and later in a multicenter international clinical phase II/III trial in 128 patients (Fx-005). In this double-blind study 20 mg/day tafamidis was compared with placebo over 18 months. The primary criteria were percentage of patients without an increase by two points of Neuropathy Impairment Score in the Lower Limbs (NIS-LL), and modification of total quality of life (TQOL). The mean age of patients was 39 years; all had a met30 TTR variant with a recent neuropathy and a median NIS-LL score in the treated group of 4/88. Most of the patients were of Portuguese origin, and were enrolled during the first 2 years of the disease. The results of the study were nonsignificant in the intention to treat group but were significant in the group of 87 patients. This was evaluable by the absence of progression of neuropathy

in 60% of patients in the tafamidis group *versus* 38% in the placebo group, and a better preserved TQOL in the tafamidis group *versus* the placebo group ( $p = 0.045$ ) [Coelho *et al.* 2012].

The French marketing authorization committee gave a favorable opinion for tafamidis (Vyndaqel, Pfizer, New York, USA) in September 2011. Tafamidis is indicated for the treatment of TTR amyloidosis in adult patients with symptomatic polyneuropathy of stage I to slow progression of the neuropathy. Many questions about tafamidis remain unanswered:

- (1) What are the longer-term outcomes, including ambulation, survival?
- (2) What is the efficacy in moderate and advanced stages of the disease or in non-met30 TTR FAP?
- (3) What is the efficacy in autonomic dysfunction?
- (4) Is tafamidis able to prevent impotence or postural hypotension?
- (5) What is the effect on cardiomyopathy?

This treatment is a disease-modifying-drug. Its most frequent side effects (very common, at least one in ten patients) are urinary tract infections and diarrhea. We do not know the long-term side effects, or its potential drug–drug interactions [Coelho *et al.* 2012].

France is the first country to obtain marketing authorization for tafamidis. The availability of tafamidis has allowed modification of the care of patients with FAP with stage I disease, enabling them to benefit from an anti-amyloid treatment as soon as the diagnosis is made. Until now, it was necessary to wait 6–12 months for LT. This alternative treatment also enables patients with FAP and contraindications to LT [age > 70 years (a third of patients), evolutive cancer] to benefit from anti-amyloid therapy [Adams *et al.* 2012b] (Figure 2).

Indications for available anti-amyloid therapies (LT, tafamidis) depend on the stage of the disease, the age of the patient, associated diseases, severity of cardiopathy and contraindications for LT [Adams *et al.* 2012a].

Tafamidis is preferential for treating early stage symptomatic FAP. Neuropathy must be symptomatic, with amyloidogenic mutant TTR (according to molecular biology study), and amyloidosis proven by biopsy, and stage I of the disease

(walking without a cane). Treatment should be initiated and monitored by a physician knowledgeable in the management of patients with TTR amyloid polyneuropathy. Physicians should continue to assess the need for other therapy, including LT, as part of the standard of care. Patients should benefit from complete neurological assessment (clinical, neurophysiological, nerve conduction study in the four limbs), cardiac assessment and periodic assessment (at least every 6 months).

The conditions for renewal of prescription every 6 months are a good safety profile and absence of significant progress of the disease. Women of child-bearing potential should use appropriate contraception when taking tafamidis. Significant criteria for progress of the neuropathy are worsening of ambulation (increase of a modified polyneuropathy disability score by one point) (Table 2), onset of orthostatic hypotension or impotence, progress of cardiopathy with worsening of stage of cardiac insufficiency (one point on the New York Heart Association classification system) or worsening of conduction disorders [Adams *et al.* 2012a]. If neuropathy or cardiopathy progresses significantly, LT or another therapeutic protocol [short interfering RNA (siRNA), antisense oligonucleotide (ASO), etc.] should be proposed when available (Table 3).

## Other therapeutic perspectives

### Transthyretin kinetic stabilizer: diflunisal

Diflunisal, a nonsteroidal anti-inflammatory drug (NSAID) which binds to T4 binding sites of tetrameric TTR, stabilizes TTR and suppresses formation of amyloid fibrils [Miller *et al.* 2004]. A randomized, controlled study against placebo is ongoing to determine if diflunisal is able to modify progression of neurological disease in FAP. A total of 130 patients of varied age and TTR mutations were enrolled. Until now, very few complications in the NSAID group have occurred. Data collection will be realized by the end of 2012 [Berk *et al.* 2011].

### Doxycycline–taurodesoxycholic acid

A combination of doxycycline and taurodesoxycholic acid (TUDCA) has been tested on transgenic mice for 15–30 days and it allowed suppression of TTR deposits in most of the old mice. The combination seems to have a synergistic action which acts during many steps of

amyloidogenesis and tissular-induced damage [Cardoso *et al.* 2010]. Doxycycline acts primarily as a fibril disrupter *in vitro*. TUDCA, a biliary acid, acts as a potent antiapoptotic and antioxidant with the ability to reduce the toxic aggregates of TTR by 75% in young transgenic mice for human V30M TTR in a TTR null background.

Twenty patients have been enrolled in a phase II study [Obici *et al.* 2012]. Seven patients have completed 1 year of treatment. Safety is good and several patients are stable at 1 year.

### Gene silencing

Gene silencing has been developed to block hepatic synthesis of both mutant and wild type TTR.

#### *Antisense oligonucleotides*

ASOs are short synthetic strings of nucleotides designed to prevent the expression of a targeted protein by selectively binding to the RNA that encodes the targeted protein, thereby preventing translation. ASOs have already been tested clinically for the treatment of viral diseases, cancer and metabolic diseases. Several recent clinical studies have documented that the antisense concept works in humans. ISIS-TTR<sub>RX</sub> is a second-generation antisense inhibitor of the molecular target TTR. ISIS-TTR<sub>RX</sub> is designed to bind within the nontranslated portion of the human TTR mRNA and results in the degradation of TTR mRNA, preventing production of both wild type and mutant TTR protein. When tested in a human TTR transgenic mouse model, ISIS-TTR<sub>RX</sub> showed a dose-dependent reduction of human TTR (up to 80%) at both the mRNA and protein levels in the serum after subcutaneous injection [Benson *et al.* 2006]. More recently, ISIS-TTR<sub>RX</sub> showed a dose-dependent reduction of human TTR in cerebrospinal fluid after intraventricular administration of ASO by suppression of choroid TTR expression [Benson *et al.* 2010]. Liver TTR mRNA and plasma TTR protein levels were also reduced by around 80% after 12 weeks of treatment in monkeys using subcutaneous injection. ISIS-TTR<sub>RX</sub> treatment was well tolerated in both rodents and monkeys and is currently under evaluation in a phase I clinical trial in normal healthy volunteers. ISIS-TTR<sub>RX</sub> will initially be developed for patients with FAP and a randomized, double-blind,

placebo-controlled study to assess the long-term safety and efficacy of ISIS-TTR<sub>RX</sub> in patients with FAP will be initiated in 2013 [Ackermann *et al.* 2012].

#### *Small interfering RNA*

ALN-TTR01 is a systemically administered lipid nanoparticle formulation of a siRNA targeting wild type and all mutant forms of TTR. This formulation delivers the siRNA predominantly to the liver, thereby inhibiting TTR synthesis at the primary site of production. In transgenic mice expressing the human met30 transgene in a heat shock transcription factor 1 null background, ALN-TTR01 led to a robust reduction of hepatic TTR mRNA levels in the liver and TTR protein levels in the circulation, and significant regression of TTR protein in the peripheral nervous system and gut. These results demonstrate the potential therapeutic benefit of ALN-TTR01 for the treatment of TTR amyloidosis (ATTR). A phase I randomized, single-blind, placebo-controlled clinical trial of ALN-TTR01 was conducted in Portugal, Sweden, the United Kingdom and France. A phase II study with multiple injections of siRNA should begin soon [Coelho *et al.* 2011].

#### *Antiserum amyloid P monoclonal antibodies*

Another strategy consists of enhancing the clearance of amyloid deposits with monoclonal antibody against human serum amyloid P component (hu-SAPMab), a ubiquitous nonfibrillar plasma glycoprotein in amyloid deposits. Administration of hu-SAPMab to mice with amyloid deposits containing hu-SAP triggers a potent complement-dependent, macrophage-derived giant cell reaction that swiftly removes massive visceral amyloid deposits. This strategy has been efficient in an experimental model of human systemic amyloid A (AA) amyloidosis with splenic and hepatic AA protein, induced by chronic inflammation in C57BL/6 mice deficient in mouse SAP but transgenic for human SAP. This therapy could be applicable to TTR FAP [Bodin *et al.* 2010].

### What are the future challenges in familial amyloid polyneuropathy?

#### Inclusion of patients with familial amyloid polyneuropathy in clinical trials

After the era of LT which has transformed the course and prognosis of neuropathy and



survival in early onset Val30met TTR FAP, a new era has opened for patients with FAP: anti-amyloid medicines. Alternative therapies are required because FAP in nonendemic areas are usually late onset cases with a late diagnosis [Adams *et al.* 2012b], who usually have contraindications to LT. It is highly recommended that patients with FAP who cannot access LT or tafamidis are enrolled in multicenter clinical trials of phase I, II or III when available to assess both the safety and efficiency of medicines developed by biotechnology organizations.

Each country must pursue its efforts to identify new cases of FAP by training and raising awareness of physicians via national referral centers and eventually national networks for FAP [Adams *et al.* 2012b].

#### Familial screening

Genetic counseling is crucial when proposing presymptomatic screening. That concerns as a priority the sibship for this disease of autosomal transmission. Screening of carriers of genetic abnormalities can identify individuals who are at risk of developing a peripheral neuropathy but also a cardiomyopathy latent for a very long time. Only accurate cardiac screening will characterize a frequent indolent cardiomyopathy. For patients with early onset FAP, it is possible to propose prenatal screening.

#### Conclusion

FAP is an excellent example of the considerable progress which has been made during the last two decades in the development of innovative therapies, including LT, which is still the reference. Current and new medicines in development issued from biotechnology organizations have the main goal of stopping or slowing down the progression of this neurodegenerative polyneuropathy. Their efficacy in treating other organs, especially the heart, must also be carefully assessed. Care of patients with FAP must be multidisciplinary in a referral center. With the help of referral centers for FAP and eventually a national network, we hope that all newly diagnosed cases of FAP will benefit from these therapeutic advances.

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#### Conflict of interest statement

The author has acted as a consultant for Alnylam and ISIS and has participated in a symposium for Pfizer.

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