Drugs
DOI 10.1007/s40265-014-0339-9

ADIS DRUG EVALUATION

Alipogene Tiparvovec: A Review of Its Use in Adults with Familial Lipoprotein Lipase Deficiency

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Abstract Alipogene tiparvovec (Glybera®; AMT-011, AAV1-LPL^{S447X}) is an adeno-associated virus serotype 1-based gene therapy for adult patients with familial lipoprotein lipase (LPL) deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. It is administered as a one-time series of intramuscular injections in the legs. LPLD, a rare autosomal recessive disorder, results in hyperchylomicronaemia and severe hypertriglyceridaemia, which in turn, are associated with an increased risk of clinical complications, the most debilitating of which is recurrent severe and potentially life-threatening pancreatitis. In clinical studies ($n = 27$ patients), one-time administration of alipogene tiparvovec was associated with significant reductions in plasma triglyceride levels during the 12 or 14 week study period post administration. Although triglyceride levels returned to pre-treatment levels within 16–26 weeks after administration, patients had sustained improvements in postprandial chylomicron metabolism, with sustained expression of functional copies of the *LPL*^{S477X} gene and of biologically active LPL in skeletal muscle. Moreover, after up to 6 years' follow-up post administration, there were clinically relevant reductions in the incidence of documented pancreatitis and acute abdominal pain events consistent with pancreatitis. Alipogene tiparvovec was generally well tolerated, with most adverse events being localized, transient, mild to moderate injection-site reactions. This article reviews the pharmacology of alipogene tiparvovec and its efficacy and safety in adults with LPLD.

Alipogene Tiparvovec in adults with familial lipoprotein lipase deficiency: a summary

Contains the gain-of-function *S447X* variant of the human *LPL* gene (LPL^{S447X}) in an adeno-associated virus vector
Significant but transient reductions in fasting plasma triglyceride (TG) levels after a one-time series of intramuscular injections
Sustained *LPL*^{S447X} expression in muscle and improvements in TG-rich lipoprotein characteristics and postprandial chylomicron metabolism
Clinically relevant decreases in incidences of pancreatitis and acute abdominal pain events consistent with pancreatitis (≤6 years' follow-up)
Generally well tolerated

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1 Introduction

Lipoprotein lipase (LPL) deficiency (LPLD) is a rare autosomal recessive disease caused by loss-of-function

Published online: 06 January 2015

mutations in the gene encoding LPL (a pivotal enzyme in lipoprotein metabolism after fat intake) or by mutations in other genes encoding proteins or enzymes that directly affect LPL function [1]. The disease is characterized by hyperchylomicronaemia and severe hypertriglyceridaemia, which in turn, are associated with an increased risk of clinical complications, including diabetes mellitus [1–4]. However, the most debilitating clinical manifestation of the disease is recurrent, severe and potentially life-threatening acute pancreatitis, with severe hypertriglyceridaemia being one of the primary risk factors for pancreatitis and the third leading cause of acute pancreatitis [2–4]. Pancreatitis is associated with an increased risk of pancreatic cancer [5] and results in significant morbidity and mortality in 20–30 % of patients, impacting on health-related quality-of-life and placing a significant economic burden on healthcare systems [3, 4].

Current strategies for the management for LPLD aim to reduce triglyceride (TG) levels close to normal levels, thereby reducing the risk of pancreatitis, and include reducing dietary fat to <20 % of the daily caloric intake or <20 g of total fat per day and the use of medium-chain TGs [1, 6]. However, life-long adherence to this very restrictive diet is extremely difficult, with many individuals with LPLD remaining at increased risk for pancreatitis and other serious sequelae [4]. In general, established TG-lowering drugs (e.g. niacin and the fibrates) have not been effective in reducing TGs in patients with LPLD [1, 4]. It is also unlikely that enzyme replacement therapy will be effective in lowering TGs in this patient population, since LPL protein has a short intravascular half-life (≈15 min) [1, 4]. Given the lack of an effective treatment for LPLD, gene replacement therapy provides a novel approach to its management [1, 4, 7]. One such approach is based on the direct in vivo administration of copies of a functional *LPL* gene variant into the muscle tissue of patients with LPLD caused by loss-of-function mutations in the *LPL* gene [1].

Alipogene tiparvovec (Glybera®; AMT-011; AAV1-LPL^{S447X}) is an adeno-associated virus (AAV) serotype 1 (AAV1)-based gene therapy that results in the expression of the naturally occurring, gain-of-function *S447X* variant of the human *LPL* gene (*LPL*^{S447X}) and subsequent synthesis and secretion of biologically active LPL [1, 4, 8]. The gene variant *LPL*^{S477X} occurs naturally in ≈20 % of Caucasians. Unlike most other LPL gene mutations that result in a loss-of-function, the *LPL*^{S447X} gene mutation is associated with several gain-of-function effects, including reduced TG levels, increased high-density lipoprotein (HDL) levels, enhanced conversion of TG-rich lipoproteins, increased LPL-mediated apolipoprotein B100 levels and an apparent reduction in the risk of cardiovascular disease, albeit the exact mechanisms of this cardioprotective effect remains to be determined [1, 8, 9]. With its approval in the EU for use in adult patients with confirmed LPLD [10], alipogene tiparvovec became the first gene therapy to be approved in the Western world [11, 12]. This article reviews the pharmacology, efficacy and safety of alipogene tiparvovec in adults with LPLD.

2 Pharmacodynamic Properties

Alipogene tiparvovec is produced using insect cells and recombinant baculovirus technology [1]. It consists of a transgenic expression cassette encoding the human *LPL* gene variant *LPL*^{S447X}, with this cassette encapsulated within AAV1 capsids [1]. The transgenic expression cassette carrying the cytomegalovirus immediate early promoter that drives expression of the human *LPL* gene variant *LPL*^{S447X} also contains a woodchuck hepatitis virus post-transcriptional regulatory element and a bovine growth hormone polyadenylation site. The entire cassette is surrounded by AAV2-derived inverted terminal repeats. By encapsulating this AAV-LPL^{S447X} capsid in an AAV1 protein shell, the efficiency of transduction of the human *LPL* gene variant *LPL*^{S447X} in skeletal muscle cells is enhanced [1].

2.1 Mechanism of Action

In proof-of-principle preclinical studies using LPL-deficient animal models, after a single series of intramuscular injections of alipogene tiparvovec, expression of the AAV1-LPL^{S447X} genome persisted in muscle cells as stable episomal concatemers for the lifetime of the cell and resulted in the synthesis of biologically active LPL [1, 12–17]. This, in turn, resulted in reduced levels of plasma TGs and complete resolution of lipaemia [1, 12–17]. For example, compared with the transfer of wild-type LPL, there was a more than twofold increase ($p < 0.01$) in plasma HDL levels and almost threefold decrease in TG levels after administration of AAV1-LPL^{S447X} in LPL–/LPL– mice deficient in LPL expression [17], with these beneficial effects persisting for more than 1 year after a single treatment [16].

In clinical studies in patients with LPLD, a single series of intramuscular injections of alipogene tiparvovec resulted in sustained expression of functional copies of the *LPL*^{S477X} gene in muscle and biologically active LPL [1, 18, 19]. The effects of alipogene tiparvovec therapy on lipid profiles in these clinical studies are discussed in Sect. 4.

A concern with AAV vectors is the potential to integrate into host mammalian genomes, albeit with a low frequency, and thereby increase the risk of tumours (as observed in preclinical studies in mice) [20, 21].

Integration-site analysis of DNA samples collected from muscle tissue of five patients with LPLD treated with intramuscular alipogene tiparvovec and from mice treated with AAVI-LPL^{S477X} indicated that there was no preferential integration of AAVI-LPL^{S477X} within genes, CpG islands, palindromic sequences or ribosomal DNA loci [20]. Notably, AAVI-LPL^{S477X} preferentially integrated into hotspots in mitochondrial DNA, with no significant accumulation of AAVI-LPL^{S477X} in the *AAVS1* locus (the preferential target of wild-type AAV1). Overall, the integration frequency with AAV vectors is markedly below that of integration-competent retroviral vectors, with AAVI-LPL^{S477X} gene therapy considered to be unlikely to be associated with adverse effects as a consequence of integration into the host genome [20]. Further support for the minimal/lack of tumorigenic potential of AAV vectors, especially when administered in tissues that divide relatively slowly such as muscle, is provided by the more than 200 individuals who have received recombinant AAV (rAAV) vectors, none of whom have developed any tumours [21].

2.2 Immunogenicity

In clinical trials, all patients with LPLD had detectable antibody responses against the protein shell of alipogene tiparvovec post therapy, despite the use of immunosuppressants [1, 8, 10, 18, 19, 22]. However, the presence of pre-existing and treatment-emergent anti-AAV antibodies did not alter sustained expression of the LPL transgene, impair the biological activity of the expressed LPL protein or impact on safety [23, 24]. Antibodies against the AAV protein shell were present prior to initiation of gene therapy in 18 of 27 participants [10], reflecting that most individuals are exposed to AAV during their lifetime [23]. After alipogene tiparvovec therapy, anti-AAV antibodies were detectable in all patients and, if already present, increased in level [10].

No participants in clinical trials had pre-existing anti-LPL antibodies or developed anti-LPL antibodies after administration of alipogene tiparvovec [23]. Use of alipogene tiparvovec is restricted to patients with detectable levels of LPL protein to avoid possible reactions against the transgene [25].

AAV vector-mediated gene transfer is also associated with local T cell-mediated immune responses to the AAV vector, albeit the long-term clinical relevance of these responses remains to be fully elucidated [21, 23, 26–28]. T-cell responses against AAV were detected in approximately one-half of patients after alipogene tiparvovec therapy; of note, no patients had detectable T-cell responses to LPL [10, 18, 23]. T-cell responses against AAV had no apparent impact on the safety or efficacy of alipogene tiparvovec or on the sustained expression of the transgene [23, 24]. After alipogene tiparvovec treatment, there appeared to be no clinical consequences of these T cell responses, with most pre- and post-exposure values for markers of clinical signs and symptoms of inflammation (e.g. creatinine phosphokinase levels, C-reactive protein levels and neutrophil counts) remaining within the normal range [24].

3 Pharmacokinetic Properties

No conventional pharmacokinetic/pharmacodynamic studies were conducted, which is considered acceptable for a gene therapy product and a rare orphan condition [25]. In humans, biodistribution data for alipogene tiparvovec are restricted to muscle tissue, with viral shedding data obtained from patients with LPLD participating in interventional clinical studies. Degradation of protein from alipogene tiparvovec is expected to occur via endogenous protein catabolic pathways [10].

After administration of alipogene tiparvovec in patients with LPLD, high levels of vector DNA in injected leg muscle, but not in non-injected muscle (low or undetectable levels), persisted for up to 12 months; no muscle biopsies have been obtained after this timepoint [10]. The highest vector DNA levels were detected in the serum (assessed using viral shedding), with clearance of vector DNA occurring at a rate of 1–2 logs per week. Based on viral shedding analyses, vector DNA was detectable in urine for up to 10 weeks, saliva for up to 12 weeks and semen for up to 26 weeks after alipogene tiparvovec therapy. There is a theoretical risk that coadministration of immunosuppressants may result in longer persistence of vector DNA in the serum and to longer shedding in saliva, urine and semen [10]; to date, longer persistence of vector DNA in the serum has not been observed in any patient after administration of alipogene tiparvovec.

4 Clinical Efficacy

The clinical efficacy of alipogene tiparvovec administered as a one-time series of intramuscular injections into the lower limbs in adults with familial LPLD and severe hypertriglyceridaemia was evaluated in three interventional, open-label trials ($n = 27$ patients) conducted in the Netherlands (CT-AMT-010-01) and in Canada (CT-AMT-011-01 and CT-AMT-011-02) [18, 19, 29]. Large studies in this patient population are not feasible because of the rare nature of the disorder. The initial efficacy assessment phases were 12–14 weeks in duration, with safety follow-up ongoing and expected to continue for up to 15 years [4].

The CT-AMT-011-03 (retrospective and prospective design) [1, 4] and CT-AMT-011-05 (retrospective; abstract presentation) [30] studies assessed the incidence and characteristics of pancreatitis and abdominal pain in patients with LPLD.

In CT-AMT-010-01, an initial proof-of-concept study, the administered AAV1-LPL^{S447X} product was manufactured using a plasmid-based process in human embryonic kidney HEK293 cells [4, 19]. All other studies reviewed in this section used AAV1-LPL^{S447X} manufactured using a baculovirus-based process in insect cells [10].

4.1 Effects on Lipids and Clinical Outcomes

4.1.1 Study CT-AMT-010-01

In the initial 12-week, interventional CT-AMT-010-01 study, patients with LPLD received AAV1-LPL^{S447X} at a dose of 1×10^{11} genome copies/kg ($n = 4$; low-dose group) or 3×10^{11} genome copies/kg ($n = 4$; higher-dose group), given as a one-time series of 40 or 60 intramuscular injections, respectively, in the leg [19]. At baseline, patients had a median plasma TG level of >14 mmol/L.

At week 12, a reduction in median fasting TG level to ≤10 mmol/L or a reduction in median fasting plasma TG levels of ≥40 % (primary endpoint; achievement of one of these parameters) was achieved by one patient in the low-dose group and three patients in the higher-dose groups after administration of AAV1-LPL^{S447X} [19]. At week 12, median TG levels were significantly ($p < 0.007$) reduced from baseline in all patients, with respective mean reductions in TG levels of 27 and 41 % in the low-dose and higher-dose groups. After 18–31 months' follow-up, plasma TG levels were no longer significantly lower than baseline levels. At 12 weeks, there were no changes from baseline in muscle function tests or in magnetic resonance image-assessed muscle fat content. Based on these findings, subsequent studies utilized higher vector doses of AAV1-based therapy, typically with concomitant immunosuppressants [19].

4.1.2 Study CT-AMT-011-01

The 12-week, open-label, dose-escalation CT-AMT-011-01 study evaluated alipogene tiparvovec in 14 patients with severe hypertriglyceridemia due to LPLD and a history of pancreatitis, with patients followed-up for more than 2 years [18]. The first two patients received alipogene tiparvovec at a dose of 3×10^{11} genome copies/kg without immunosuppressants, the next four patients received alipogene tiparvovec at a dose of 3×10^{11} genome copies/kg in combination with oral ciclosporin and mycophenolate mofetil (taken for 12 weeks from the day after alipogene tiparvovec administration) and the remaining eight patients received alipogene tiparvovec at a dose of 1×10^{12} genome copies/kg in combination with the same immunosuppressant regimen. The primary objectives were safety and the percentage of patients achieving ≥40 % reduction in median fasting plasma TG 3–12 weeks after alipogene tiparvovec therapy. At baseline, patients had a median fasting plasma TG level of ≥13 mmol/L [18].

At weeks 3–12, 50 % of patients had achieved a reduction in median fasting TG level of ≥40 %, with median TG levels reduced from baseline by an average of 39.5 % in all but two patients [18]. Reductions from baseline in TG levels during weeks 3–12 were significant in the overall population ($p = 0.0009$) and in the alipogene tiparvovec 1×10^{12} genome copies/kg group ($p = 0.0023$). Four patients achieved a reduction in TG level to ≤10 mmol/L. Although TG levels tended to increase towards pre-treatment levels ≈16–26 weeks after alipogene tiparvovec therapy, there was a reduction in the TG and cholesterol content of chylomicrons. In seven evaluable muscle biopsies, expression of LPL^{S447X} persisted 26 weeks after alipogene tiparvovec therapy, with three samples testing positive for LPL protein and five showing an increase in intracellular lipids consistent with LPL activity [18]. As reported in the European summary of product characteristics [10], the 1×10^{12} genome copies/kg dose of alipogene tiparvovec appears to be the optimal dose, based on results from this study [18].

After up to 2 years' follow-up, most patients continued to experience improvements in self-assessed clinical symptoms such as the capacity to eat more food or food they were unable to eat prior to treatment, increased energy levels and less abdominal discomfort [18].

4.1.3 Study CT-AMT-011-02

Based on results from the CT-AMT-010-01 (Sect. 4.1.1) and CT-AMT-011-01 (Sect. 4.1.2) trials, the 14-week, phase II/III CT-AMT-011-02 study was initiated [29]. This study in five patients with LPLD and a history of pancreatitis evaluated the effects of alipogene tiparvovec on postprandial chylomicron metabolism and appearance rates of plasma nonesterified free fatty acid (NEFA) and glycerol. Alipogene tiparvovec was administered at a dose of 1×10^{12} genome copies/kg and given in combination with oral immunosuppressants [29].

Postprandial chylomicron metabolism was assessed over a 24-h period and appearance rates for plasma NEFA and glycerol were assessed over a 9-h period after ingestion of a standard liquid low-fat test meal, with these parameters assessed 2 weeks before alipogene tiparvovec administration and at weeks 14 and 52 after alipogene tiparvovec therapy [25, 29]. Blood sampling was performed every hour, starting 1 h before and continuing until up to 24 h after ingestion of the meal, during which time all patients

received a continuous infusion of radiolabeled-palmitate tracer (incorporated into the chylomicron particles as core TG) and a primed infusion of radiolabeled glycerol tracer. At enrolment, all patients had a baseline TG level of >11 mmol/L, no patients were receiving lipid-lowering drugs and two patients had type 1 diabetes [29].

Alipogene tiparvovec gene therapy was associated with a significant improvement in postprandial chylomicron metabolism at 14 weeks, with no change in glycerol and NEFA appearance rates over this post-administration period [29]. At 14 weeks, postprandial mean total plasma TG levels were reduced by ≈60 % (7.30 vs. 18.77 mmol/L prior to alipogene tiparvovec; $p < 0.001$), with significant ($p < 0.001$) reductions in postprandial mean chylomicron TG (by ≈85 %) and the chylomicron-TG/total plasma TG ratio (0.15 vs. 0.64 prior to alipogene tiparvovec). The chylomicron-TG/total plasma TG ratio assesses the average buoyancy of plasma TG, with large/buoyant chylomicrons considered the most pathogenic chylomicrons and causal in eliciting pancreatitis. At 14 weeks, there were also significant ($p < 0.05$) reductions from pre-administration values in postprandial peak chylomicron activity at 6 h (by 79 %) and for the 24-h area under the curve for chylomicron activity (by 93 %) [29]. Two weeks prior to administration of alipogene tiparvovec, the postprandial peak chylomicron level was delayed in patients with LPLD compared with individuals with normal LPL activity (10 vs. ≈3 h), which most likely reflected delayed clearance and an accumulation of chylomicrons [25]. In patients with LPLD, a delay of ≈10 h in the postprandial chylomicron peak persisted at 52 weeks ($n = 3$ evaluable) [29].

There were no significant changes in postprandial plasma glucose, insulin and C-peptide levels 14 weeks after administration of alipogene tiparvovec compared with pre-administration levels [29].

After alipogene tiparvovec therapy, long-term transgene expression and biological effects (i.e. LPL protein activity and improved chylomicron metabolism) were observed at 52 weeks' follow-up (abstract presentation) [31].

4.2 Effects on the Risk of Pancreatitis

Study CT-AMT-011-03 [25, 32], a retrospective, pooled analysis of data from participants in the interventional CT-AMT-011-01 [18] and CT-AMT-011-02 [29] trials ($n = 17$ evaluable) and the Preparation-02 observational study ($n = 5$ evaluable patients with LPLD) [8], was designed to evaluate the incidence and severity of acute abdominal pain pancreatitis episodes in patients with LPLD. Historical data for all acute abdominal pain events leading to hospital presentation/admission were retrieved, with pancreatitis defined according to Revised Atlanta Diagnostic Criteria by an independent peer review panel that were blinded as to whether subjects had been treated with alipogene tiparvovec and whether events occurred before or after alipogene tiparvovec administration [25]. The following categories were used: definite pancreatitis, probable pancreatitis and acute abdominal pain; events that could not be classified as such were categorized as other events. A Cox regression analysis for time-between-event data was used to estimate the risk for pancreatitis and permit comparison of periods of different lengths (e.g. historic control with post alipogene tiparvovec treatment); event risk rather than the actual number of events was compared. The median post treatment follow-up period was ≈3 years. Sensitivity analyses showed that results of the Cox regression analysis were consistent when 1-year periods between 3 and 10 years prior to alipogene tiparvovec were used as a control [25].

In Cox regression analyses, there were significant reductions in the risk of definite and probable pancreatitis events (combined categories) after administration of alipogene tiparvovec versus historical controls, with hazard ratios (HRs) ranging from 0.31 to 0.38 ($p < 0.05$) [25]. When definite pancreatitis, probable pancreatitis and abdominal pain events were combined, the risk of pancreatitis episodes in the post-treatment period was reduced to 56–67 % ($p < 0.02$). After treatment, there was also a trend towards shorter median hospital stays in cases of hospitalization for events categorized as definite pancreatitis (median 0 vs. 28 days pre-treatment), probable pancreatitis (median 0 vs. 0 days), abdominal pain (median 0 vs. 3 days) and other (median 0 vs. 12 days). None of these pancreatic events were severe, with no patients admitted to intensive care units for any of these events [25].

There was a reduction in the risk of pancreatitis after up to 6 years' follow-up post administration of alipogene tiparvovec gene therapy in patients with LPLD in the CT-AMT-011-05 study ($n = 13$) [30]. At a median follow-up of 5.8 years after a single administration of alipogene tiparvovec, the hospitalization rate for pancreatitis was 59 % lower than pre-treatment, with a 54 % reduction in the rate of hospitalizations for pancreatitis plus abdominal pain events consistent with pancreatitis (Fig. 1). None of these pancreatic events were considered to be severe [30].

5 Safety Profile

Alipogene tiparvovec was generally well tolerated in interventional clinical studies discussed in Sect. 4 [1, 18] and after long-term follow-up of up to 6 years [30]. No dose-limiting toxicities were reported [1, 18]. The most common adverse events were immediate local injection-site reactions, including oedema, pain in the legs and myalgia, and were of mild to moderate intensity and resolved within a few days [1]. Pain in the extremity in the days after administration was

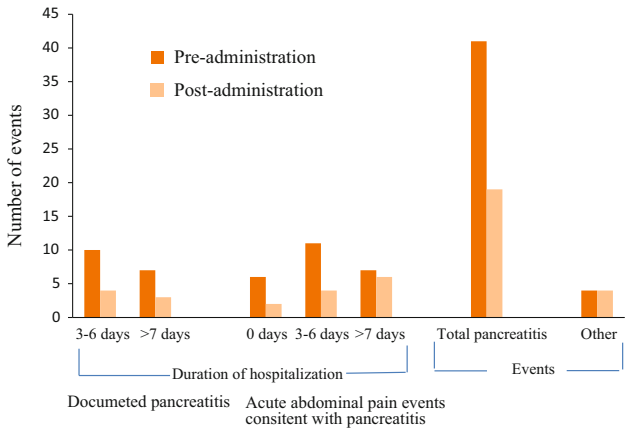

Fig. 1 Frequency of documented pancreatitis and acute abdominal pain events consistent with pancreatitis occurring during up to 6 years' follow-up after one-time administration of alipogene tiparvovec in adults with lipoprotein lipase deficiency [30]

experienced by about one-third of adults who received alipogene tiparvovec in clinical trials [10].

Adverse reactions occurring after alipogene tiparvovec administration that were categorized as very common (frequency ≥10 %) included headache, pain in extremity, fatigue, hyperthermia and contusion [10]. Common adverse reactions (frequency ≥1 to <10 %) included decreased appetite, hypoglycaemia, burning sensation, dizziness, lipaemia retinalis, hypertension, pulmonary embolism, abdominal pain, xanthoma, chills and injection site reactions. A pulmonary embolism occurred in one patient 7 weeks after the administration of alipogene tiparvovec [10], which was considered unlikely to be related to alipogene tiparvovec therapy or LPLD.

6 Dosage and Administration

Alipogene tiparvovec was approved under exceptional circumstances consistent with the rarity of LPLD and based on its efficacy and safety in the specified population for which it is approved [25]. It is approved for adult patients with familial LPLD and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions [10]. The diagnosis of LPLD has to be confirmed by genetic testing, with the indication restricted to patients with detectable levels of LPL protein. Alipogene tiparvovec should be administered by trained dedicated experts as a single one-time series of intramuscular injections in the legs (maximum total dose of 1×10^{12} genome copies/kg administered as multiple injections of 1.5×10^{12} genome copies). It must not be administered intravenously [10].

Treatment should be monitored by measuring neutralizing antibodies and T-cell responses against AAV1 and LPL^{S447X} at baseline and at 6 and 12 months after administration of alipogene tiparvovec [10]. From 3 days before and for 12 weeks after administration of alipogene tiparvovec, an immunosuppressant regimen of ciclosporin (3 mg/kg/day) and mycophenolate mofetil (2×1 g/day) is recommended. In addition, 30 min before administration of alipogene tiparvovec, an intravenous bolus injection of methylprednisolone 1 mg/kg should be administered because of the number of injections required.

Local prescribing information should be consulted for detailed information regarding the use of alipogene tiparvovec in specific patient populations, contraindications, warnings, precautions and administration.

7 Current Status of Alipogene Tiparvovec in Familial Lipoprotein Lipase Deficiency

LPLD is an orphan disease for which there was previously no available treatment [33]. Alipogene tiparvovec therapy was designed to restore deficient LPL function via transfer of a gain-of-function LPL gene variant into muscle cells of patients with LPLD in order to normalize TG and chylomicron levels [25].

In clinical studies in patients with LPLD, one-time administration of alipogene tiparvovec was associated with significant reductions (by ≈40–60 %) in plasma TG levels during the 12 or 14 week study period after administration (Sect. 4). Although TG levels generally returned to pre-treatment levels within 16–26 weeks post administration, patients had sustained improvements in postprandial chylomicron metabolism, with sustained expression of functional copies of the $LPLS^{477X}$ gene in injected muscle and of biologically active LPL at 52 weeks' follow-up. Moreover, after up to 6 years' follow-up post administration, there were clinically relevant decreases in the incidence of documented pancreatitis and acute abdominal pain events consistent with pancreatitis (Sect. 4.2). Although these results are based on retrospective analyses, all of which have inherent limitations, the rarity of LPLD makes it almost impossible to undertake a comprehensive clinical assessment with a controlled study on pancreatitis reduction [25]. Alipogene tiparvovec was generally well tolerated in clinical studies, with most events being localized, transient, mild to moderate injection-site reactions, and no dose-related toxicities reported (Sect. 5).

AAV vectors have several advantages as gene transfer vectors, including a lack of association of wild-type AAV with known diseases and pathology in humans, the requirement for a helper virus such as adenovirus to replicate, stable integration of wild-type AAV into the host cell genome at a specific site (AAVS1) with minimal risk for random integration into the genome, low immunogenic potential and an ability to infect quiescent cells [23]. These considerations along with the apparent good tolerability

and safety profile of rAAV vectors means that they are currently considered the vector of choice for treating inherited diseases of post-mitotic tissues [21].

Conversely, concerns have been raised regarding specific issues with rAAV vectors such as the tumorigenic potential and the impact that AAV vector-induced humoral and cellular immune responses have on efficacy and safety [23, 34]. Although concerns have been raised regarding the tumorigenic potential of AAV vectors, as observed in some preclinical animal studies, alipogene tiparvovec and other rAAV vectors appear to have a minimal tumorigenic potential, particularly when administered into slowly dividing tissues such as muscle (Sect. 2.1). The occurrence of cellular and humoral immune responses to rAAV vectors is dependent upon a number of factors, including the route of administration, target tissue, vector serotype and dose, disease targeted and expression level of the transgene [23]. With alipogene tiparvovec therapy, these immune responses did not alter sustained expression of the LPL transgene, impair the biological activity of the expressed LPL protein or appear to impact on the safety of alipogene tiparvovec therapy (Sect. 2.2).

With its approval in the EU, alipogene tiparvovec is the first gene therapy to be approved in the Western world and, as such, represents a significant step forward and sets a precedent for future gene therapy development. Alipogene tiparvovec is in pre-registration in several other countries, including the USA and Canada, for use in patients with LPLD [33]. Given the rarity of the disease, clinical experience with alipogene tiparvovec is limited. Further clinical use of alipogene tiparvovec should help to more fully define the long-term efficacy and safety of this novel gene therapy. An LPLD patient registry has been set up in Europe to provide a better understanding of this rare disease and collect long-term safety data on one-time alipogene tiparvovec therapy.

Data selection sources: Relevant medical literature (including published and unpublished data) on alipogene tiparvovec was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 8 Dec 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Alipogene tiparvovec, Glybera, AMT-011, AAV1-LPL^{S447X}, lipoprotein lipase, lipoprotein lipase deficiency, hyperlipoproteinemia type 1, hyperlipidaemia, pancreatitis.
Study selection: Studies in adult patients with lipoprotein lipase deficiency who received alipogene tiparvovec. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Disclosure The preparation of this review was not supported by any external funding. Lesley Scott is a salaried employee of Adis/Springer. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the authors on the basis of scientific and editorial merit.

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