Integrated product development for ATMPs

Advanced Therapy Medicinal Products (ATMPs), which include cell and gene therapies and tissue engineered products, are a group of innovative products targeting diseases and conditions for which there are few, if any, effective treatments. The success of the first CD19 chimeric antigen receptor T cell (CAR T) products Kymriah and Yescarta against B-cell malignancies has raised the awareness of the high potential of ATMPs, but also shown the several challenges relating to their clinical use[1]. One of these challenges is the high prices asked by the developers of these products, which are not always supported by national pricing and reimbursement bodies[2].

In such cases, the discrepancy between a regulatory approval and a negative decision from a health technology assessment (HTA) body has raised concerns and questions from industry about how to ensure that an approved product also gets to the market and to patients. Many jurisdictions have created early access schemes and ways to communicate with regulatory and HTA bodies early on to ensure successful outcomes of both reviews[3]. However, the ATMP industry is facing challenges in both aspects.

The development of ATMPs has substantially increased, with a focus on clinical trials in recent years. Several cell and gene therapy products have been authorised worldwide, most recently the CAR T cell product Tecartus from Kite Pharma Inc[4] in the US and Zolgensma for spinal muscular atrophy (SMA)[5] in the EU.

Today there are more than 980 developers globally, the majority (78%) of whom are in North America and Europe.[6] Over 1,000 clinical trials were underway worldwide at the end of 2019, almost two-thirds (64%) of which were in Phases 2 and 3. There has been a clear shift from early to late phase trials, as only four years earlier the majority of trials (> 90%) were in Phases 1 and 2[7]. Since the beginning of 2015, the overall number of ATMP clinical trials and ATMPs in Phase 3 has doubled, suggesting multiple new ATMPs will be approaching the marketing authorisation application stage in the next few years.

Today, the focus of ATMP development is heavily in gene therapy and genetically modified cells which constitute three quarters of products in clinical trials. This is most probably due to the fast development of novel vectors and technologies, including genome editing. In addition, a lot of safety data has accumulated for certain gene therapy approaches (e.g. adeno-associated virus vectors, AAV and lentivirus vectors, LVV), which reduces the regulatory burden before first clinical trials.

From an indication perspective, the majority of ATMP clinical trials (657/1066, 62%)[6] are in oncology, including leukaemia, lymphoma, and solid tumours, which may be explained by the great interest towards novel immunotherapies using genetically modified cells. In 2019, genome edited cells using the CRISPR/Cas9 approach proceeded to clinical trials both in the US and the EU[8] and the first results from a trial studying an induced pluripotent stem (iPS) cell-derived product were reported in the EU[9].

ATMPs as medicinal products

The first approved CAR T products and *ex vivo* gene therapy products for monogenic diseases have shown outstanding efficacy results, thus moving towards corrective treatments for these diseases instead of pharmacotherapies that only treat disease symptoms. However, ATMPs are complex medicinal products with specific risks and challenges. Both cell and gene therapy products have unique safety features that may be difficult to anticipate before human exposure[1]. Amongst the common risks are infections (caused by microbial contamination of starting/raw materials or during processing); tumourigenicity, due to cell transformation or integrational mutagenesis, replication competent viral impurities, virus reactivation, unwanted immunogenicity or rejection, ectopic engraftment of cells to non-target tissues, on-target and off-target toxicities (especially genome editing), treatment failures, and viral shedding.

The manipulation of cells and the use of modified, recombinant nucleic acids/viruses may also bear unknown risks, which may not be solvable through standardisation and/or quality control. To identify and mitigate possible risks of ATMPs during development, a risk-based approach is recommended by CAT/EMA.[10] One of the biggest challenges posed by ATMPs is the inherent variability of the starting materials, especially where viable cells are used. If the variability is not controlled and starting materials are not defined by acceptance criteria, the product quality may, in the worst case, impact safety and efficacy outcomes. In addition, the manufacturing processes for ATMPs are complex and may need novel analytical solutions to control consistency, product quality and comparability, should there be any changes to the process.[11]

Due to the nature of ATMPs (e.g. cells, viruses), it is not possible to terminally sterilise these products and thus the sterility has to be built in through aseptic processing, sterility of the raw materials and the microbiological purity of the starting materials. This will require defined testing and control of all materials and premises. Non-clinical studies may also pose challenges, as suitable disease models are rarely available and the extrapolation of results from standard non-clinical safety tests using e.g. rodents may be hampered by differences at the cellular and molecular level between species[10].

The first approved ATMPs have also thrown up challenges in clinical evidence generation, especially with respect to efficacy data and long-term safety. Single arm clinical trials in small populations may not provide a sufficiently strong basis for a benefit/risk evaluation and the identification of an appropriate comparator may turn out to be difficult or even impossible. In such cases, companies may have used historical /observational evidence, where it is difficult to be objective. Use of surrogate endpoints may further hamper the assessment of efficacy and long-term effectiveness. Therefore, early risk identification and the careful design of clinical studies are strongly recommended.[12] Organisation of service delivery within the health care systems may also need special

TABLE 1 Pricing and reimbursement of recently approved ATMPs in the US and EU

Product	Indication	Dosing	Approval	Price	Pricing rule
Kymriah/Novartis CD19 CAR T cells	B-ALL DLBCL	Single dose	US 2017 US 2018 EU 2018	$475,000 (B-ALL) $373,000 (DLBCL) €320,000[3]	Outcome-based[1]
Yescarta/Kite/Gilead CD19 CAR T cells	DLBCL, PMBCL	Single dose	US 2017 EU 2018	$373,000 €327,000	Value-based[2]
Luxturna/Spark Therapeutics AAV2- hRPE65	Vision loss due to Leber congenital amaurosis or retinitis pigmentosa	Single dose	US 2017 EU 2018	$850,000 per patient[3] $746,000 per patient[4]	Outcome-based and instalment[5]
Aloficel/Takeda Mesenchymal stromal cells	Treatment of anal fistulas in adults with Crohn's disease	Four-dose treatment	EU 2018	€60,000 ($67,000)	Value-based
Zolgensma/Avexis AAV9-hSMN	Spinal muscular atrophy (SMA)	Single dose	US 2019	$2.1 million $425,000 per year for 5 consecutive years	Outcome-based and instalment
Zynteglo/Bluebird Bio Autologous CD34+ cells expressing beta A-T87Q-globin gene	Transfusion dependent beta - thalassemia	Single dose	EU 2019	€1.575 million ($1.77 million), upfront payment €315,000, four consecutive payments, if successful	Outcome-based and instalment

1 Reimbursed only if patients experienced a complete response within defined timeframe
2 Company to reimburse part or all of the cost of the drug if patients using it do not see improvement
3 Undisclosed discounts reported
4 Reported for UK
5 Instalment models expect demonstration of short-term efficacy and long-term durability to earn reimbursement, payments can be spread over several years
AAV= adeno-associated virus, B-ALL= B-cell acute lymphoblastic leukemia, CAR = chimeric antigen receptor, CD = cluster of differentiation, DLBCL = diffuse large B-cell lymphoma, hRPE65= human retinal pigment epithelium 65 kDa protein, hSMN = human Survival Motor Neuron protein, PMBCL= primary mediastinal large B-cell lymphoma

consideration before commercialisation.

The prices of the first approved ATMPs have been high and not always supported by the HTA authorities.[3] One challenge when assessing the value of ATMPs is the overall understanding and knowledge about the novel products, especially when they are curative and not for symptomatic treatment. ATMPs involve complex technologies with strong effectiveness and new methods are needed to value remission of a severe disease, impact on disease progression/disease modification, eradication of disease or true cure, when no alternative treatment options exist.

The HTA review involves the handling of uncertainty for highly innovative products and thus, it is critical that the clinical evidence is generated in a good and reliable manner for cost-effectiveness review [13]. The clinical studies for ATMPs are fairly short compared with expectations of long-term, perhaps lifelong, effects. Thus, the available data may not be sufficient for evaluation of long-term benefit and can increase the uncertainty of the HTA. There are also significant challenges in managing reimbursement of products with very high unit prices, which has led to novel risk-sharing and payment models to ensure financial sustainability of the healthcare systems.[14]

The regulatory assessment is always data-driven and the agreed indication is based on the population(s), for which a positive benefit/risk profile is generated through clinical studies. The regulatory review, performed in the EU by Committees for Advanced Therapies (CAT) and Human Medicinal Products (CHMP), includes an assessment of the CMC data, including characterisation, manufacturing and quality control strategy, production consistency and comparability results. In addition, non-clinical and clinical studies are assessed to verify the pharmacodynamic and pharmacokinetic properties of the product and the available safety and efficacy data for the benefit/risk evaluation, including justification of the proposed dosing and indication.

Clinical endpoints are expected to capture the safety and efficacy of the product in the chosen patient population; the final opinion is based on the overall benefit/risk profile. In principle, multiple products may be approved for the same indication, with the exception of orphan products, for which significant benefit over an existing product(s) must be demonstrated if the developer would like to maintain the benefits associated with an orphan designation, i.e. defined period of market exclusivity. The regulatory review also takes into account the severity of the disease, available treatment options for the disease, tolerability of the new and existing products and the convenience of the medication for patients. However, the cost associated with the products does not play any role in the regulatory review.

The HTA review is always a comparison of the new product against existing treatment options and an assessment of the cost/benefit of the product. The review is based on clinical studies, which should demonstrate the long-term benefit and cost-effectiveness of the product.

In the EU, the HTA evaluation is performed by national HTA authorities in each member country, examples being the Federal Joint Committee in Germany and National

Institute for Health and Care Excellence (NICE) in the UK. Differences in HTA rulings between jurisdictions have been reported[15], which can hamper reimbursement negotiations for innovative products. However, different collaboration and harmonisation activities at the EU level (EUNetHTA) and globally by WHO[16] are underway with the aim of alleviating the differences in reimbursement decisions. Reimbursement decisions are most often based on cost per QALY (quality-adjusted life year) and there are different thresholds used for different products. Usually the highest price levels are accepted for orphan drugs and curative products. Key data for the HTA review are those from clinical studies. Trial endpoints should provide appropriate information for QALY calculations. For the regulatory review, clinical studies are conducted in a controlled manner establishing efficacy of the product in the studied population. For the HTA review, there is a need to gain information about whether a product works similarly in clinical practice as it did in a trial setting, and if it provides a more effective use of available resources. The cost of innovation can be high, and may need risk sharing between industry and payers, especially in cases where the long-term effectiveness and safety of the product may be unknown.

Pricing and reimbursement

Recent approvals for Kymriah and Yescarta, Luxturna, Aloficel, Zolgensma and Zynteglo have raised the issue of the affordability of innovative medicines and paved the way towards novel risk-sharing models for pricing and reimbursement (Table 1). For Kymriah and Yescarta, a single payment was set, however both Novartis and Kite/Gilead have agreed to risk sharing agreements[17] and/or fee reductions[18] with payers. In May 2019, a Japanese government panel approved a price of $305,800 for Kymriah.[19] Yescarta has not been approved yet in Japan. For both CAR T products, HTA authorities have acknowledged uncertainties and limited datasets from the products' single arm trials and have recommended a reassessment when more clinical and economic data are available.

Luxturna was found to lead to significant vision improvement for patients in the regulatory and HTA assessments[4, 20]. The price was set at $425,000 per eye in the US ($850,000 per patient), whereas the first price reported in Europe (UK) was over $100,000 lower per patient due to a discount applied through Britain's National Health Service. On the other hand, the clinical evidence for Aloficel was found to not be convincing to support the original price in the EU[21] set by Takeda. The company later announced that it will reimburse part or all of the cost of the expensive drug if patients using them do not see an improvement.

For Zolgensma and Zynteglo, the announced prices reached new records at $2.1 and $1.77 million respectively. For both products, instalment plans with a low upfront payment and subsequent annual fees have been set, which are dependent on the long-term effectiveness of the product. Given the concerns payers and HTA bodies have towards the pricing of ATMPs, it is critical for developers to be aware of recent studies in the field. Further information can be gained e.g. through International Society for Pharmacoeconomics and Outcomes Research (ISPOR), which has a special task force on methodology development around value frameworks, focusing on pricing.

Evidence generation for market access purposes should be based on traditional methods, taking into consideration the specificities and challenges of ATMPs. One should also consider the HTA reviews/decisions available for ATMPs and the identified differences between HTA bodies and payers.[22] High unit prices are a challenge for health care systems and the affordability of expensive products, especially if targeting large patient groups, needs to be taken into account when planning a reimbursement strategy. As for all new medicines, it is critical to de-risk and validate the strategy with the relevant HTA bodies through scientific advice and by reviewing recent updates on HTA methodology and the implications for similar products. For ATMPs, the long-term risks and outcomes are still fairly unknown.

Current expedited licensing pathways may turn out to be counterproductive from an HTA perspective, and result in a significant regulatory burden after authorisation in the event that confirmatory clinical studies are required. Therefore companies are advised to seek joint regulatory/HTA scientific advice early in order to agree on valid controls and endpoints, to identify uncertainties of long-term effects and to discuss the use of registries and real world evidence for both regulatory and HTA reviews. For orphan drugs, the data may be convincing but may apply to very few patients; in such cases it may be challenging to prove the actual benefit of the new treatment option.

For novel ATMPs, it may be relevant to ask for feedback from healthcare professionals and patient representatives to properly justify the value of a new product. Payer market research may give further understanding of the attractiveness of a specific target product profile (TPP) and what needs to be considered when developing the evidence base. One may also need to explore innovative financial payment models like annuity, amortisation or discount models and consider the value building needed for risk-sharing agreements[23, 24]. A robust process of early planning for receiving reimbursement is highly recommended.

Integrated product development

ATMPs are complex medicinal products, for which the identification of the active substance, mode of action, functionality and potency assays, consistent manufacturing processes and generation of robust non-clinical and clinical data may be challenging. For such products, it is imperative to ensure that the product design meets the intended clinical use and that all limitations and risks are well understood, including the impact of co-medications, interfering substances and routes of administration. The design of clinical studies should ensure that the data can be used both for regulatory and HTA purposes. Due to the inherent variability and complexity of the starting materials (cells, tissues, viruses etc.) the quality, safety and efficacy of ATMPs are interlinked. Thus, the CMC development should be well advanced before pivotal non-clinical and clinical studies take place. In addition, a proper risk analysis is required before the start of key non-clinical safety studies, including the availability/feasibility of relevant animal models, dose finding and biodistribution, good laboratory practice (GLP) requirements, specific risks and mitigation strategies.

Often a gap analysis of available CMC/non-clinical/clinical

data is helpful before making regulatory submissions to understand the possible pitfalls. In the event that changes to the manufacturing process and/or controls are required during clinical development, the comparability of the different versions of the product must be assessed. The same approach is expected when moving from non-clinical toxicology studies to a first in man study. Therefore it is recommended to use the product produced under good manufacturing practice (GMP) for non-clinical GLP studies. Equally important is to plan for HTA activities before pivotal clinical study(ies) and to establish contacts with regulatory and HTA authorities to understand missing data and additional studies/data that may be required for licensing and market access. Post-authorisation risk mitigation strategies and follow-up tools like registries and pharmacovigilance activities should be also considered.

Conclusions

ATMPs face the same regulatory and HTA challenges as every new medicinal product, but exaggerated due to their specific characteristics and limitations. Often there is a high upfront cost per patient based on data from a small number of patients. This increases the uncertainties for cost/effectiveness calculations. For ATMPs, de-risking the development programme is essential, and thus an integrated product development strategy is recommended in order to meet both regulatory and HTA requirements. Developers should also seek early dialogue with regulatory and relevant HTA bodies to discuss data requirements, possible new payment models and thus ensure successful licensing and market access.

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