Assessing the future: evaluation of the initial HTA assessments of ATMPs in the Nordics

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Background and Objectives

The first cell- and gene therapies, so called advanced therapy medicinal products (ATMPs), have recently become available, making it possible to treat, and even potentially cure, very severe and sometimes previously untreatable conditions such as advanced blood cancers and hereditary genetic diseases. Over the next few years many more innovative ATMP therapies are expected to gain marketing authorization with limited data and very high initial costs per patient. As of October 14, 2019, four cell- and gene therapies have been assessed by two or more reimbursement agencies in the Nordic countries; the Dental and Pharmaceutical Benefits Agency (Tandvårds och Läkemedelsförmånsverket, TLV), the Norwegian Medicines Agency (Statens Legemiddelsverk, SLV), the Finnish Medicines Agency (Fimea) and the Danish Medicines Council (Medicinrådet, DMC).

The aim was to assess the first ATMP reimbursement agency appraisals in the Nordic setting with particular consideration to time to patient access, judgement of clinical value and judgement of cost-effectiveness.

Methods

Publicly available assessment reports were retrieved from each reimbursement agency's website and from the website of institutions providing recommendation for usage in the Nordics (i.e. the Swedish New Therapies (NT)-council, the Norwegian Decision Forum and the Council for Choices in Health Care in Finland (COHERE)).

Results

These four ATMPs have been (or are being) assessed by the Nordic reimbursement agencies:

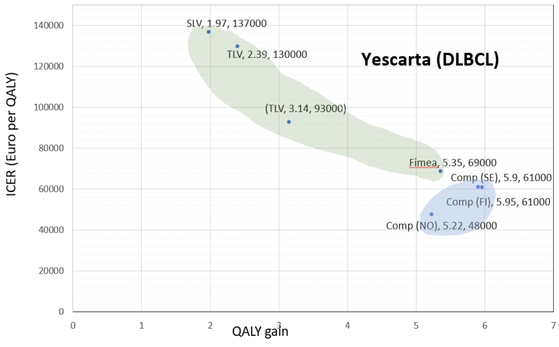
- darvadstrocel (Alofisel) for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy.
- voretigen neparvovek (Luxturna), for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.
- tisagenlecleucel (Kymriah) for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse, and the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
- axicabtagene ciloleucel (Yescarta) for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Assessment of Yescarta

The disease severity of DLBCL and PMBCL was assessed as very high across agencies and the absolute shortfall was estimated to 15.5 (QALYs) by SLV.

The clinical assessment was based on ZUMA, an open, single-arm, phase II trial. The treatment was considered effective although there were uncertainties with respect to the relative effectiveness, duration of response and long-term effect due to clinical trial related factors such as short follow-up, small sample size, lack of direct comparison and high degree of censoring and patient heterogeneity between data sources (the phase II trial and a retrospective study on chemotherapy). In the health economic assessment of Yescarta versus chemotherapy, TLV, Fimea, and SLV estimated the incremental cost-effectiveness ratios (ICERs) in a similar range and approximately two to three times higher than the company estimates, mostly due to differences in judgement of long-term efficacy and quality adjusted life year (QALY) gain (Figure 1).

Figure 1: Estimated QALY gains and ICER:s for Yescarta (DLBCL) versus chemotherapy.



Note that TLV presented QALY gains and ICER:s based on two different assumptions of cure rate.
Abbreviations: Comp (SE), (FI) and (NO) are company estimates in Sweden, Finland and Norway respectively.

Assessment of Alofisel

Alofisel faced similar challenges related to uncertainties and extrapolation as Yescarta and Kymriah. SLV estimated the absolute shortfall to 9 QALYs and TLV judged the severity of the disease to be high.

The clinical assessment was based on the randomized, double-blind, placebo-controlled phase III clinical trial ADMIRE-CD. The European Medicines Agency (EMA) had previously judged the effect size to be clinically relevant albeit modest. The agencies considered the long-term efficacy (cure and risk of relapse) to be highly uncertain.

Since the severity was considered high (as opposed to very high) and the clinical efficacy less impressive the willingness to pay was lower.

In the health economic assessment of Alofisel versus a mixed treatment comparison (MTC), the company used a time horizon of 40 years which was not accepted by any agency. TLV estimated the ICER as a function of time horizon (5 to 40 years) to 65,000-224,000 EUR. SLV estimated a QALY gain of 0.45 for an 8-year time horizon and an ICER of 147,000 EUR. SLV:s and TLV:s estimates were very similar when assuming the same time horizons. When applying the same time horizon as the company, the TLV ICER estimate still differed by 60 percent.

Assessment of Luxturna

When assessing Luxturna TLV judged the severity of the disease to be high. The assessment was based on studies 301 and 302, an open, randomized phase III trial, and a follow-up where all patients received the gene-therapy. TLV considered the effect to be robustly shown for the first three years (where clinical trial data was available) and uncertain in the long-term. According to DMC, the treatment offered an important clinical value with a low quality of evidence. Compared to best supportive care (BSC), TLV estimated the QALY gain to 2.6 to 4.3 and the ICER to 168,000-280,000 EUR.

Table 1 (below) describes time from market authorization to recommendation (time to patient access) in each of the markets, ranked by the first country to issue a recommendation. Please note that the recommendation process is in most cases iterative with initial negative recommendations.

Table 1: Summary of time to patient access for advanced therapy medicinal products in the Nordic region

ATMP	Indication	Regulatory approval	Recommendation, no of months from market authorization	Assessment, no of months from market authorization
Alofisel	Complex anal fistulas	March 23rd, 2018	NT-council, 3 months (negative - Jun 2018)	TLV, 2 months (May 2018)
			DMC, 9 months (negative - Dec 2018)	DMC + Amgros, 9 months (Dec 2018)
			Decision forum, 10 months (positive, Jan 2019)	SLV, 3 months (Jun 2018)
Luxturna	Retinal dystrophy	November 22nd, 2018	DMC, 10 months (negative - Sep 2019)	DMC, 10 months (Sep 2019)
			NT council, 11 months (negative - Oct 2019)	TLV, 6 months (May 2019)
Kymriah	B-cell acute lymphoblastic leukaemia	August 22nd, 2018	Decision forum, 4 months (positive, Dec 2018)	SLV, 3 months (Nov 2018)
			DMC: 5 months (positive, Jan 2019)	DMC + Amgros, 5 months (Dec 2019)
			NT-council: 9 months (positive, May 2019)	TLV, 8 months (Apr 2019)
			COHERE, recommendation expected in Nov 2019	Fimea, 3 months (Nov 2018)
	Diffuse large B-cell lymphoma		DMC, 6 months (negative - Feb 2019)	DMC + Amgros, 6 months (Feb 2019)
			NT-council, 10 months (negative - Jun 2019)	TLV, 10 months (Jun 2019)
			Decision Forum: 13 months (negative- Sep 2019)	SLV, 10 months (Jun 2019)
			COHERE, recommendation expected in Nov 2019	Fimea, 4 months (Dec 2018)
Yescarta	Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma	August 23rd, 2018	DMC, 9 months (negative- May 2019)	DMC+ Amgros, 9 months (May 2019),
			NT-council, 13 months (positive, Sep 2019)	TLV, 3 months (Nov 2018)
			Decision forum, 13 months (negative- Sep 2019)	SLV, 10 months (Jun 2019)
			COHERE, recommendation expected in Nov 2019	Fimea, 4 months (Dec 2018)

Assessment of Kymriah

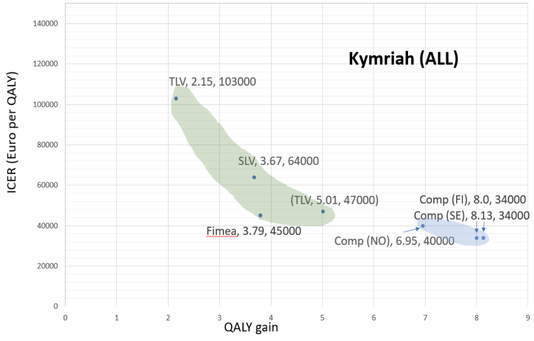
B-cell acute lymphoblastic leukaemia

The disease severity of ALL was judged to be very high across agencies and SLV estimated the absolute shortfall to 51 QALYs.

The clinical assessment was based on three open label, single-arm phase II trials, ELIANA, ENSIGN, and B2101J, and a matched-adjusted indirect comparison (MAIC). The treatment was considered effective although the effectiveness and long-term efficacy was deemed uncertain due to similar factors as in the assessment of Yescarta. Uncertainties related to assumptions on cure and mortality were stressed. SLV and DMC both noted methodological issues and challenges with the indirect comparison and DMC required a naive indirect treatment-comparison (ITC).

TLV, Fimea and SLV estimated similar QALY-gains. Company estimated QALY-gains were twice as high and consequently company base-case estimated ICERs were substantially lower (Figure 2).

Figure 2: Estimated QALY gains and ICER:s for Kymriah (ALL) versus chemotherapy.



Note that TLV judged the QALY gain and ICER to be in the green area (somewhere between the two estimates) based on uncertainties in the proportion of long-term survivors.
Abbreviations: Comp (SE), (FI) and (NO) are company estimates in Sweden, Finland and Norway respectively.

Diffuse large B-cell lymphoma (DLBCL)

The disease severity and absolute shortfall of DLBCL was judged to be the same as in the assessment of Yescarta.

The clinical assessment was based on the open-label, single-arm, phase II trial JULIET. Similar concerns as in the assessment of Yescarta were raised across the agencies. TLV deemed the uncertainties for Kymriah to be higher than for Yescarta, related to the fact that a third of the enrolled patients did not undergo treatment.

Fimea did not assess the cost-effectiveness. TLV chose not to estimate any ICER due to the uncertainties. SLV acknowledged similar uncertainties but estimated an ICER based on the intention to treat (ITT) population as well as treated patients only (mITT), which they also did for Yescarta. The ICER from SLV was twice that of the company.

Conclusions

Time from market approval to recommendation varied across the four ATMPs. In several instances, the process was iterative with initial negative recommendations and also first assessment did not translate into first positive recommendation.

The absence of direct comparisons, lack of long-term follow-up, high severity and high costs are well-known challenges from rare diseases and oncology. However, for ATMPs they are often even more pronounced.

In these first assessments the agencies adopted different ways of addressing these uncertainties by expressing the ICER as a function of crucial assumptions and/or hypothetical price reductions or rebates.

In the coming years several ATMPs are expected to enter the market. HTA assessments serve only as a first step towards introduction and are combined with payer agreements in the next step, sometimes requiring iterative approaches and additional data with times from initial assessment to agreements spanning over several months.

Methods to improve decision-making under uncertainty, flexible and structured follow-up and dynamic pricing and risk-sharing will need to develop further to accommodate these challenges.

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