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What is the value of reducing the use of scarce biological resources such as donor organs?

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Introduction

Transplant donor organs and human blood are scarce biological resources. In 2021, 41,354 transplants were performed in the US, but 116,566 patients remained on waiting lists and 6,564 died while awaiting an organ transplant. Indeed, the shortage of donor organs is the most significant global issue in the field of organ transplantation.[1]

Some pharmaceuticals can reduce or delay the need for transplants, making more organs available for transplant and reducing waiting times. However, it is unclear whether the value of reducing or postponing organ transplantation is considered by health technology assessment (HTA) agencies.

To better understand the elements that HTA agencies value in submissions of interventions indicated for terminal organ diseases, we reviewed decisions and recommendations by the UK National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) to ascertain whether these agencies value a reduction of or delay in organ transplantation and, in particular, the associated benefit to patients on waiting lists who would receive earlier organ transplants.

Methods

We identified and reviewed NICE and CADTH HTA decisions and recommendations published between 2005 and 2024 that suggested a product benefit of delayed time to organ failure or improved graft survival.

We extracted and reviewed the following key factors:

- Drug products considered
- Disease indication and area
- Endpoints of the clinical trials submitted
- Endpoints of the economic models
- Mention of organs being scarce, limited, or valuable resources
- Mention of equity issues
- Mention of avoiding, delaying, or reducing the use of donor organs

Results

Twenty-eight drug products were considered:

- Basiliximab
- Belatacept
- Dapagliflozin
- Eculizumab
- Elexacaftor + Tezacaftor + Ivacaftor and Ivacaftor
- Everolimus
- Finerenone
- Imlifidase
- Ivacaftor
- Ivacaftor +tezacaftor + elexacaftor
- Lumacaftor + ivacaftor
- Lumasiran
- Mannitol dry powder
- Maralixibat
- Mycophenolate mofetil
- Mycophenolate sodium
- Nintedanib
- Nitisinone
- Obeticholic acid
- Odevixibat
- Rabbit anti-human thymocyte immunoglobulin
- Ravulizumab
- Sirolimus
- Tacrolimus (immediate-release)
- Tacrolimus (prolonged-release)
- Targeted-release budesonide
- Tezacaftor + ivacaftor
- Tolvaptan

- Thirty-two decisions and recommendations were reviewed: 13 kidney-related, 8 liver-related, and 11 lung-related.
- A total of 71 documents were reviewed.
- Over 30 transplant-related clinical trial endpoints were identified from submissions and eight transplant-related endpoints were identified from network meta-analyses, a systematic review, and a prospective cohort RWE study.
- Five of the 32 decisions (15.6%) mentioned organs as being scarce, limited, or valuable resources.
- Nine (28.1%) mentioned equity issues.
- Nine (28.1%) mentioned avoiding, delaying, or reducing the use of donor organs; in none was this aspect of value quantified.

Table 1: Analysis of transplant-related factors in HTA decision-making

Organ	Medicine or enzyme	Therapy area	HTA agency	Mention of:		
				Organs as scarce, limited, or valuable	Equity issues	Avoiding, delaying, or reducing donor organ use
Kidney	Dapagliflozin	Chronic kidney disease	NICE		✓	
	Targeted-release budesonide	Primary IgA nephropathy	NICE		✓	✓
	Finerenone	Chronic kidney disease in type-2 diabetes	NICE		✓	
	Imlifidase	Desensitization treatment before kidney transplant in chronic kidney disease	NICE	✓	✓	✓
	Tolvaptan	Autosomal dominant polycystic kidney disease	CADTH			✓
			NICE			✓
	Immuno-suppressive therapy[a]	Immunosuppressive therapy for kidney transplant in adults	NICE		✓	
		Immunosuppressive therapy for kidney transplant in children and young people	NICE		✓	
Liver	Odevixibat	Progressive familial intrahepatic cholestasis	NICE	✓		
			CADTH		✓	
	Obeticholic acid	Primary biliary cholangitis	NICE	✓	✓	✓
			CADTH			✓
	Maralixibat	Cholestatic pruritus in patients with ALGS	CADTH	✓	✓	
Lung	Ivacaftor + tezacaftor + elexacaftor, tezacaftor + ivacaftor, and lumacaftor + ivacaftor	Cystic fibrosis	NICE	✓		✓
	Elexacaftor + tezacaftor + ivacaftor and ivacaftor	Cystic fibrosis, F508del CFTR mutation	CADTH			✓
	Elexacaftor + tezacaftor + ivacaftor and ivacaftor	Cystic fibrosis, F508del CFTR mutation, 6 years and older	CADTH			✓

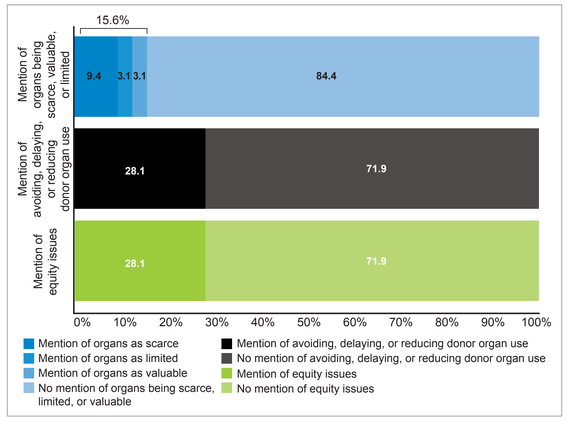
[a]Included the following drug products: basiliximab, rabbit anti-human thymocyte immunoglobulin, tacrolimus (immediate-release and prolonged-release), mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus, and belatacept. ALGS, Alagille syndrome; IgA, immunoglobulin A.

Table 2: Potential reductions in numbers of donor organs required

Product	HTA agency	Transplants avoided
Dapagliflozin	NICE	Over a period of up to 38.2 months, 3 (0.1%) patients in the dapagliflozin group vs 8 (0.4%) patients in the placebo group received a transplant.
Obeticholic acid	NICE	In the company's economic model, patients treated with OCA were found to have an 84% lower chance of undergoing liver transplant compared with patients treated with UDCA over 12 months.
Obeticholic acid	CADTH	Over a lifetime (50 years), the company's model predicted: • UDCA-intolerant population: 152 liver transplants per 1,000 patients (undiscounted) versus 39 transplants in OCA-treated patients • UDCA-tolerant population: 135 liver transplants per 1,000 patients (undiscounted) versus 38 transplants in OCA-treated patients
Nitisinone	CADTH and NICE	In the NTBC Study (time period unclear), 13% of nitisinone-treated patients vs 25% in historical control underwent a liver transplantation.
Maralixibat	CADTH	A natural history comparison study reported 67% improvement in liver TFS with maralixibat treatment compared with the GALA control group over a 6-year period.
Ivacaftor + tezacaftor + elexacaftor, tezacaftor + ivacaftor, and lumacaftor + ivacaftor	NICE and CADTH (3 indications)	The company's model predicted that introduction of the triple therapy in 2021 could lead to 146 fewer lung transplants by 2030, compared with 98 fewer transplants if the drug was introduced in 2025.
Elexacaftor + tezacaftor + ivacaftor and ivacaftor	CADTH	Prior to initiation of the triple therapy, 16 patients were waiting for a lung transplant and 37 were under consideration as transplant candidates in the next 3 months (a total of 53 patients; 22%). After 3 months' follow-up, 5 (2%) patients were on the transplant list or being considered for transplant, 2 (0.8%) had received a transplant, and 1 (0.4%) had died while awaiting transplant.
Lumacaftor + ivacaftor	NICE	The company's model predicted 1.82% of patients receiving lumacaftor + ivacaftor + SOC versus 6.8% receiving SOC would have a lung transplant in their lifetime.
Nintedanib	NICE	In the INPULSIS 1 trial, 6.9% of patients in placebo vs 5.2% in the nintedanib group died or had a lung transplant over a 52-week period.
Everolimus	NICE	The trial found that 6.7% of patients receiving everolimus + reduced tacrolimus experienced composite efficacy failure from randomization to month 12, compared with 9.7% of patients receiving tacrolimus.

GALA, Global Alagille Alliance; HR, hazard ratio; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; NTBC, nitisinone; OCA, obeticholic acid; SOC, standard of care; TFS, transplant-free survival; UDCA, ursodeoxycholic acid

Figure 1: NICE and CADTH decisions and recommendations addressing transplant-related considerations



HTA perspectives on organ value and scarcity

"The foregone benefit of providing a donated kidney to another person for whom it is suitable because of introducing imlifidase would need to be considered in decision making."

NICE committee on the value of imlifidase for preventing kidney transplant rejection in people with chronic kidney disease

"[The committee] was also aware of the scarcity of donor organs and that other patients on the transplant waiting list for other reasons might benefit if obeticholic acid were available."

NICE committee on the value of obeticholic acid for primary biliary cholangitis

"By reducing [...] the requirement for lung transplants, and transplant organs themselves, CFTR modulators would free up valuable resources for other people."

NICE committee on the value of ivacaftor + tezacaftor + elexacaftor, tezacaftor + ivacaftor, and lumacaftor + ivacaftor for cystic fibrosis

Conclusions

Even though some trials and economic models included outcomes of delayed organ failure or absolute reduction in organ transplants, our research found little evidence of any consideration by HTA agencies of the indirect benefit to patients on waiting lists who would receive an earlier transplant.

This study demonstrated that while the quality of life and cost benefits to patients treated with a specific intervention and healthcare systems of delaying or avoiding an organ transplant is discussed and/or captured within economic models, the full value and potential patient benefits of reducing or delaying organ transplantation does not appear to be considered by HTA agencies.

In the document reviewed, there were more comments from NICE committees acknowledging organs as scarce resources than from CADTH. However, the only statements identified that appeared to consider benefits to patients beyond those receiving the intervention under assessment were in NICE's appraisals of obeticholic acid and imlifidase. The latter pointed to the benefit foregone by patients receiving imlifidase, who may then be eligible for a kidney that might otherwise have gone to a different patient.

Further research is warranted to understand how the spillover value of delaying or reducing organ transplants, or reducing the use of other scarce biological resources, can be quantified in HTA submissions.

References

1. Kupiec-Weglinski JW. Donor organs for transplant and human blood are scarce resources. Frontiers in Transplantation. 2022;1:1-5. doi:https://doi.org/10.3389/frtra.2022.897679

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