

Article

A Causal Analysis of the Effect of Aucatzyl Administered to Adult Subjects with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukaemia

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Abstract

The FELIX trial is an ongoing, single-arm, open-label study without an internal control, in which adults with relapsed/refractory B-cell precursor acute lymphoblastic leukaemia receive Aucatzyl (a CAR-T cell therapy) and are followed for overall survival. Here, we combine the Toulmin form of argument with a structural causal model to assess the causal effect of Aucatzyl in the FELIX trial.

Keywords: B-cell acute lymphoblastic leukaemia; CAR-T cell therapy; overall survival; causal analysis

1. Introduction

B-cell acute lymphoblastic leukaemia (also referred to as B-cell precursor acute lymphoblastic leukaemia) is a haematological malignancy arising from clonal proliferation of abnormal B-cell precursors (B-lymphoblasts) in the bone marrow. Whilst acute lymphoblastic leukaemia in the paediatric age range is often curable, outcomes in adults are less favourable [1,2].

Current management involves chemotherapy regimens (induction, consolidation and maintenance, tailored to age and cytogenetic findings) that may be supplemented by (i) targeted therapies against CD antigens (e.g., inotuzumab ozogamicin and blinatumomab), (ii) allogeneic stem-cell transplantation for eligible patients, and (iii) radiotherapy.

Despite advances in treatment, many adults experience relapsed or refractory disease. Relapsed acute lymphoblastic leukaemia refers to patients who initially achieve remission and then develop recurrent disease, whereas refractory acute lymphoblastic leukaemia refers to cases that fail to respond to frontline therapy. Prognosis for these patients is poor, with an overall survival of approximately 15% at 12 months [3,4]. This unmet clinical need has driven the development of chimeric antigen receptor T-cell (CAR-T) therapies [4].

Aucatzyl (obecabtagene autoleucel) is a genetically modified autologous CAR-T cell therapy directed against CD19 on aberrant lymphoblasts. Evidence for efficacy is derived from the FELIX trial, an ongoing, single-arm, open-label study without an internal control, in which adults with relapsed/refractory B-cell precursor acute lymphoblastic leukaemia receive Aucatzyl and are followed for overall survival [5]. Although such designs are commonly used for rare diseases, the absence of randomisation and an internal comparator limits the ability of conventional statistical approaches to support causal inference. Therefore, alternative approaches are required to evaluate treatment effects and to differentiate association from causation.



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Here, we combine the Toulmin form of argument [6,7] with a structural causal model based on Pearl's framework [8] to conduct a causal analysis of the effect of Aucatzyl in the FELIX trial [5,9]. This approach has the advantage of making assumptions clear, supporting formal reasoning about interventions and enabling the interpretation of counterfactual outcomes in the absence of a randomised control.

2. Materials and Methods

We have previously described the Toulmin form of argument as a means of clarifying the data-generating process [10] and setting out the structure of an argument in a transparent and logically coherent manner. We now use the Toulmin form of argument to present the FELIX trial in Supplemental Material S2.

We couple the Toulmin argument to a structural causal model, as described by Pearl, constructed using a directed acyclic graph, non-parametric structural equations and counterfactual analysis [11–13]. In this approach, the Toulmin argument provides a structured narrative that complements the mathematical representation of the causal model to ensure that assumptions and supporting evidence are explicitly stated.

3. Results

3.1. Causal Inference

We now use the tools of causal inference, as described by Pearl [11–13]. These tools are applied to data from the FELIX study and external natural history estimates, as described below.

Tool 1: To encode causal information in a transparent and testable way using a structural causal model.

A structural causal model is a mathematical object that provides an interpretation of every causal query about the domain of interest. A causal model is a triple:

$$M = \langle U, V, F \rangle \quad (1)$$

where (i) U is a set of exogenous variables that are determined by factors outside the model, (ii) V is a set $\{V_1, V_2, \dots, V_n\}$ of endogenous variables that are determined by other variables in the model (both exogenous and endogenous) and (iii) F is a set of functions, where each function f maps an endogenous variable from its parent variables and exogenous factors.

A probabilistic causal model is a pair:

$$\langle M, P(u) \rangle \quad (2)$$

where M is a causal model and $P(u)$ is a probability function over the domain of U . $P(U)$ represents a summary of the state of the world outside the phenomenon of interest; the randomness encoded in $P(U)$ induces variations in the endogenous set V .

Inside the model, the value of each endogenous variable V_i is determined by a causal process, $f_i(p_{ai}, u_i) \rightarrow v_i$, that maps the exogenous factors U_i and a set of endogenous variables P_{ai} (so-called parents) to V_i . These causal processes—or mechanisms—are assumed to be invariant unless explicitly intervened upon and, together with the background factors, represent the data-generating process according to which Nature assigns values to the endogenous variables in the model.

Every structural causal model M can be associated with a directed acyclic graph $G(M)$ where each node corresponds to a variable in V and the directed edges point from a parent to a child; the graph only identifies those variables that have a direct influence on each endogenous variable; it does not specify the form of each function.

3.2. Directed Acyclic Graph

The directed acyclic graph for relapsed/refractory B-cell acute lymphoblastic leukaemia is represented by the causal chain shown in Figure 1a. The disease driver (D)—at present an unknown endogenous variable thought to act via rearrangement of genetic sequences—promotes clonal proliferation of abnormal B-cell precursors (P), leading to expansion of these cells (L) and, in turn, leukopenia, thrombocytopenia and anaemia (R). Overall survival (S) is shortened by bleeding, infection and organ failure.

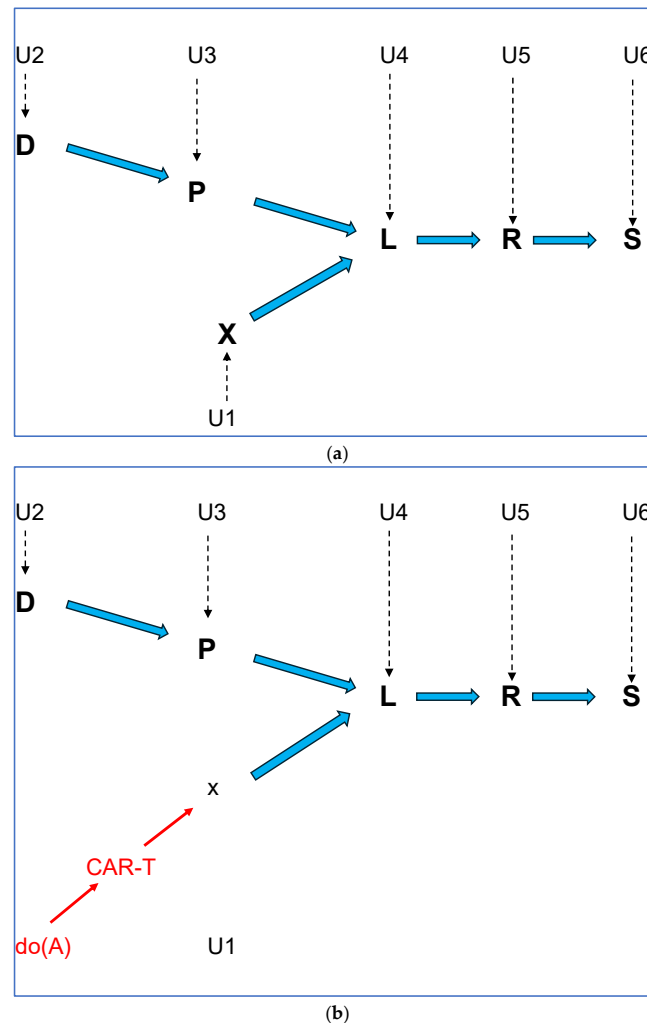


Figure 1. (a) The graph of the causal chain depicting the disease process of acute lymphoblastic leukaemia. The letters represent: D: driver for clonal proliferation of abnormal B-cell precursors. P: production of abnormal B-cell precursors. L: abnormal B-cell precursors in bone marrow. X: elimination process for abnormal B-cell precursors. R: response of the haematopoietic system. S: overall survival of the recipient, the target quantity that can be measured. U1–U6: exogenous variables. The model of (a) consists of non-parametric structural equations (autonomous functions): $f_x = (u_1)$; $f_d = (u_2)$; $f_p = (d, u_3)$; $f_l = (p, x, u_4)$; $f_r = (l, u_5)$; $f_s = (r, u_6)$. (b) The “surgically modified” sub-graph (of the causal chain shown in (a)) depicting overall survival in study participants who have been administered Aucatzyl. The letters represent: D: driver for clonal proliferation of abnormal B-cell precursors. P: production of abnormal B-cell precursors. L: abnormal B-cell precursors in bone marrow. do(A): intervention (do-operator) representing administration of Aucatzyl, a known exogenous variable. CAR-T: circulation and expansion of CAR-T cells that seek cells bearing the CD19 motif. X: elimination process for abnormal B-cell precursors driven by Aucatzyl. R: response of the haematopoietic system (either complete response, incomplete response or no response). S: overall survival of the recipient, the target quantity that can be measured; U1–U6: exogenous variables (the pre-existing connection between U1 and X has been severed and replaced by $do(A) \rightarrow CAR-T \rightarrow X$).

The graph of Figure 1a lies on layer 1 of Pearl's causal hierarchy [14,15] and represents an observed state upon which we may make inferences. The causal chain reflects our current understanding of the disease process in acute lymphoblastic leukaemia.

Tool 2: To predict the effects of actions using *do*-calculus.

Layer 2 of Pearl's hierarchy [14,15] allows one to represent the notion of “doing,” i.e., intervening (acting) in the world to bring about some state of affairs by taking advantage of the invariant characteristics of structural equations and by defining and estimating causal effects in non-linear, non-parametric models where the functional forms of the equations are unknown. This is done through a mathematical operator called *do*(*x*) which simulates physical interventions by deleting certain functions from the model, by replacing them by a constant $X = x$ whilst keeping the rest of the model unchanged.

An intervention on a causal model represents an external force that fixes a variable to a constant value and is denoted *do*($X = x$), meaning that *X* is fixed to the value *x* and is described by the sub-model *M_x* where:

$$M_x = \langle U, V, F_x \rangle \quad (3)$$

This transformation from *M* to *M_x* modifies the algebraic content of *F* to *F_x* by deleting from *F* all functions corresponding to *X* and replacing them with a set of functions $X = x$ with the implicit assumption that *F_x* possesses a unique solution for every *u*. This transformation is also represented graphically by severing all pre-existing in-bound edges to *X* in *G*(*M*) and replacing them with the in-bound intervention where $X = x$ so resulting in a “surgically modified (interventional) sub-graph” *G*(*M_x*). The minimal modification $X = x$ takes place without making inconsistent the system of equations associated with the sub-model.

Here, we ask the question “what if we intervene and boost the activity of *X* by administration of Aucatzyl?”

Figure 1b depicts administration of Aucatzyl (*do*(*A*)) to adult subjects with relapsed/refractory B-cell acute lymphoblastic leukaemia, leading to expansion of CAR-T cells (CAR-T) and increased elimination of CD19-expressing lymphoblasts (*X*, *L*). The response of the haematopoietic system (*R*) then determines overall survival (*S*).

Note that, according to the model, if CAR-T cells wane in efficacy over time, then the driver for clonal expansion (*D*) will again dominate and disease will recur.

The sub-model of Figure 1b consists of non-parametric structural equations (autonomous functions): $f_x = (do(A), CAR-T)$; $f_d = (u_2)$; $f_p = (d, u_3)$; $f_l = (p, x, u_4)$; $f_r = (l, u_5)$; $f_s = (r, u_6)$. The intervention represented in Figure 1b is informed by observed clinical effects of Aucatzyl such as expansion of CAR-T cells, reduction in lymphoblast burden and subsequent haematopoietic recovery as reflected in response categories (CR, CRi, no response) reported in the FELIX trial.

Tool 3: To compute counterfactuals and find cause of effect.

Layer 3 of Pearl's hierarchy [14,15] permits use of retrospection and thinking about alternative ways the world could be to find “cause of effect.” Three counterfactual quantities have been described where causation has two aspects: necessity and sufficiency, i.e., some conditions are necessary (needed for something to happen), while other conditions are sufficient (enough to make something happen) [16]. In this case, the “something to happen” is overall survival after administration of Aucatzyl.

We assume monotonicity, consistency and exogeneity [16] where (i) monotonicity assumes that the outcome of improved overall survival is monotonic relative to administration of Aucatzyl, i.e., exposure to Aucatzyl does not cause an increase in mortality, (ii) consistency expresses the assumption that responses to treatment rely entirely on bi-

ological factors and are unaffected by settings where treatment takes place and (iii) the CAR-T cell product is an exogenous component of the explanatory model.

We identify probabilities of interest [16] as follows: X and Y are two binary variables in a causal model: X is the input (administration of AUCATZYL) and Y is the output (overall survival); let x and y stand for the propositions $X = \text{true}$ and $Y = \text{true}$, respectively; let x' and y' be their respective complements.

Under the circumstances of exogeneity and monotonicity, the probability of necessity (PN), probability of sufficiency (PS) and probability of necessity and sufficiency (PNS) are identifiable and are given by the following equations:

$$PN = (P(y|x) - P(y|x'))/P(y|x) \quad (4)$$

In words, PN stands for the probability that event y would not have occurred in the absence of event x , given that x and y did in fact occur. The probability of necessity is a measure of when something is required for something to happen, i.e., a measure of attribution.

$$PS = (P(y|x) - P(y|x'))/(1 - P(y|x')) \quad (5)$$

In words, PS stands for the probability that setting x would produce y in a situation where x and y are in fact absent. The probability of sufficiency is a measure of when something is adequate for something to happen.

$$PNS = P(y|x) - P(y|x') \quad (6)$$

In words, PNS stands for the probability that Y will occur if and only if X has taken place. The probability of necessity and sufficiency is the risk difference (in this case for overall survival at 12 months after exposure to product) between persons exposed to the AUCATZYL and persons not exposed to AUCATZYL.

Using the above equations in this case:

- $P(y|x)$ is the probability of survival at 12 months after administration of AUCATZYL.
- $P(y|x')$ is the probability of survival of adults with relapsed/refractory acute lymphoblastic leukaemia if AUCATZYL had not been administered; from natural history studies, this probability is about 15% at 12 months [3,4].

Table 1 summarises the probabilities of “necessity,” “sufficiency” and “necessity and sufficiency” for those participants in the FELIX trial who achieved (i) complete remission, (ii) complete remission with incomplete haematologic recovery and (iii) for those who did not respond with survival probabilities of approximately 78%, 45% and 14%, respectively, as estimated from reconstructed Kaplan–Meier data (Supplementary Material S1). These values were substituted into Equations (4)–(6) together with the natural history estimate (15%) to calculate PN, PS and PNS for each subgroup.

The probability of necessity and sufficiency among AUCATZYL-treated participants who achieved complete remission and survived to 12 months was 63%, which was higher than that observed in the other response groups.

Note that the probability of necessity, the probability of sufficiency and the probability of necessity and sufficiency are global features of a causal model; they do not depend on the structure of the process mediating cause and effect. The probability of necessity and sufficiency is a measure of benefit, and these data suggest that the greatest benefit occurs in those achieving complete remission, followed by those achieving CRi, with no evidence of benefit in non-responders.

Tool 4: To ask about the mechanism by computing direct and indirect effects.

What is the mechanism by which exposure to AUCATZYL leads to improved overall survival? Does AUCATZYL act “directly” or does AUCATZYL act “indirectly” via a mediator? In order to address this question, we need a sensitive ability to tease apart direct effects (which do not pass through a mediator) and indirect effects (which do). Here, we use the method of Pearl [17] that relies on counterfactual argument to approach the issues of “direct” and “indirect” effects separately and where the mediator is allowed to choose its “natural” value.

Table 1. The probabilities of necessity, sufficiency and necessity-and-sufficiency for participants in the FELIX trial with relapsed/refractory acute lymphoblastic leukaemia who are alive at 12 months after administration of AUCATZYL. Values were calculated using data in the Supplementary Materials.

	For Those Who Achieve Complete Remission (CR)	For Those Who Achieve Complete Remission with Incomplete Haematologic Recovery (CRi)	For Those Who Do Not Respond (Not CR/Not CRi)
Probability of necessity (PN)	81%	67%	0%
Probability of sufficiency (PS)	74%	35%	0%
Probability of necessity and sufficiency (PNS)	63%	30%	0%

3.3. Analysis of Mediation

The term “direct effect” is meant to quantify an influence that is not mediated by other variables in the model, i.e., the sensitivity of Y to changes in X while all other factors in the analysis are held fixed.

“Indirect effects,” on the other hand, cannot be defined in the manner applied to “direct effects” because it is impossible to hold a set of variables constant in such a way that the effect of X on Y measured under those conditions would circumvent the direct pathway, if such exists.

In order to overcome this obstacle, we use operational meanings of “direct effect” and “indirect effect” with the path-switching technique of Pearl [17]; this technique permits the evaluation of direct and indirect effects in non-linear, non-parametric models of “non-experimental” data as are found in clinical trials that are not randomised, not controlled and unblinded. The analysis requires conditions that are always satisfied by Markovian models (a chain of modelled events where the probability of each event transition depends only on the state reached of the previous event; there is no “memory” beyond the previous event) of which directed acyclic graphs are examples. Thus, in counterfactual language:

- An event $X = x$ is said to have a direct effect on variable Y in situation $U = u$ if the following inequality holds:

$$Y_{x^*}(u) \neq Y_{x, Mx^*(u)}(u) \quad (7)$$

In words, the value of Y under $X = x^*$ differs from its value under $X = x$ even when we keep M at the same value ($Mx^*(u)$) that M attains under $X = x^*$.

- An event $X = x$ is said to have an indirect effect on variable Y in situation $U = u$ if the following inequality holds:

$$Y_{x^*}(u) \neq Y_{x^*, Mx(u)}(u) \quad (8)$$

In words, the value of Y changes when we keep X fixed at $X = x^*$ and change M to a new value, $Mx(u)$, the same value that M would attain under $X = x$.

We use the directed acyclic graph in Figure 2 to illustrate the causal relationships among circulating CAR-T cells, haematopoietic response and overall survival. Visual inspection suggests no common-cause variable (confounder) of the mediator–outcome relationship is represented in this simplified diagram.

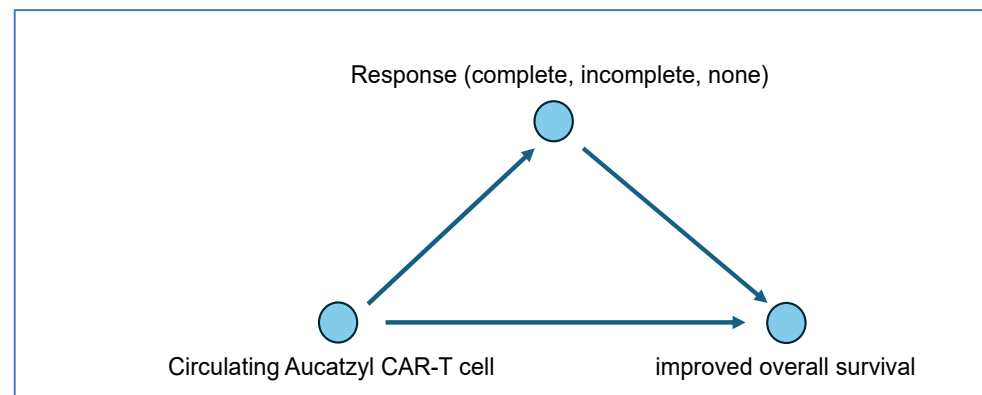


Figure 2. Causal diagram to investigate to what extent the effect of Aucatzyt on improved overall survival is direct or indirect via the response of the haematopoietic system.

Let X represent circulating CAR-T cells; let M represent the mediator, response; and let Y represent improved overall survival.

To examine for a direct effect, we hold the mediator (M) constant and vary X by “one unit.” We start from the absence of circulating CAR-T cells (X), where lymphoblasts are present in high numbers. We administer Aucatzyt to achieve a “one unit” increase in X ; we now look at individuals who show “no response” (i.e., persistent high lymphoblast burden). In this subgroup, overall survival is 14% at 1 year, similar to the natural history of the condition. These observations do not support a direct effect.

To examine for an indirect effect, we hold X constant and vary the mediator (M). We start with individuals who received Aucatzyt but exhibited “no response,” with overall survival of 14% at 1 year. We then consider those exposed to Aucatzyt who achieved a “complete response,” defined by <5% lymphoblasts among nucleated bone-marrow cells and peripheral blood measurements within reference intervals. In this subgroup, overall survival is 86% at 1 year, substantially higher than the natural history estimate. These observations are consistent with improved 1-year overall survival being mediated indirectly via haematopoietic response following exposure to Aucatzyt and circulating CAR-T cells.

In the absence of evidence for a direct effect, the total effect of Aucatzyt-associated CAR-T cell expansion is inferred to arise through an indirect pathway via haematopoietic response—most evident with complete response, less evident with incomplete response and not evident in non-responders.

Tool 5: To transfer learnings.

The above structural causal model has been developed for one environment; we may extend the model to embrace new environments through use of do-calculus and selection diagrams (so-called “data fusion”) [18]. Examples of new environments would be a registry of patients or patients exposed to Aucatzyt outside of a clinical trial. Data from new environments are not yet available to permit an exercise in data fusion.

Tool 6: To recover from missing data by determining what can be estimated “as if no data were missing.”

All participants in the main efficacy analysis population of the clinical trial were administered Aucatzyt; overall survival was calculated from the date of first Aucatzyt infusion to the date of death. Patients still alive were censored at the date of last contact.

If the date of death was missing then death was imputed to the maximum of the full (non-imputed) last contact date. If the date that the subject was last known to be alive was missing then being alive was imputed to the last-known date.

Two subjects were found to meet the important protocol deviation of missing disease assessments; given that there were only 2 subjects in this category and because the missing data did not impinge upon the data for overall survival then we did not conduct further testing [19,20].

Tool 7: To confirm “actual cause.”

In the confirmation of “actual cause,” we have used the Halpern-Pearl model for which three criteria must be fulfilled [21,22].

Criterion 1 for “actual cause”: administration of product and outcome of improved overall survival for those who display “complete remission” are both present so fulfilling criterion 1.

Criterion 2 for “actual cause”: in this case, the structural causal model is represented by a causal chain and so criterion 2 reduces to a “but-for” statement. Thus: participants who responded to exposure to Aucatzyl with “no response” displayed an 86% probability of demise within 1 year. Most participants in the trial would have died over the course of 1 year follow-up but for the administration of Aucatzyl producing a “complete response.” Criterion 2 is considered fulfilled.

Criterion 3 for “actual cause”: we assume the minimality condition wherein the cause does not have any irrelevant or trivial components. Criterion 3 is considered fulfilled.

All three criteria are considered fulfilled and so we hold that the “actual cause” of improved overall survival over the 1-year follow-up period in participants of the trial was the administration of Aucatzyl resulting in a “complete remission.”

Tool 8: To make personalised decisions.

How would an individual react if given treatment or if denied treatment? Since an individual cannot be subject to both treatment and its denial, response functions must be inferred from population data. To this effect, four types of individuals are described by benefit, immune, doom and harm [23,24].

Let us denote the variable X as treatment where x and x' represent respectively treatment and no treatment. And let us denote the variable Y as recovery where y and y' represent respectively recovery and no recovery. We further use y_x to denote the counterfactual sentence “Variable Y would have the value y had X been x .”

- $P(\text{benefit})$: probability that an individual would survive over the course of 12 months if administered Aucatzyl x and would die if not administered Aucatzyl.

$$P(\text{benefit}) \triangleq P(y_x, y'_{x'}) \quad (9)$$

In causal analysis, the probability of benefit is a measure of efficacy and is equal to the probability of necessity and sufficiency (PNS).

- $P(\text{immune})$: probability that an individual would survive for 12 months after administration of Aucatzyl regardless of being administered Aucatzyl or not.

$$P(\text{immune}) \triangleq P(y_x, y_{x'}) \quad (10)$$

- $P(\text{doom})$: probability that an individual would die within 12 months regardless of being administered Aucatzyl or not.

$$P(\text{doomed}) \triangleq P(y'_{x'}, y'_{x'}) \quad (11)$$

and

- P(harm): probability that administration of Aucatzyl will harm an individual. In this context, harm denotes promotion of demise within 12 months after administration of Aucatzyl.

$$P(\text{harm}) \triangleq P(y'_{x'} | y_{x'}). \quad (12)$$

Here, where there is monotonicity (it is assumed that Aucatzyl does not promote death) then harm equals zero for all three subgroups of response (CR, CRi, not CR/not CRi) to exposure to Aucatzyl. Monotonicity also facilitates identification of the probabilities of causation as displayed in Table 2.

Table 2. Probabilities of benefit, being immune and being doomed at 12 months after administration of Aucatzyl for participants in the FELIX study with relapsed/refractory acute lymphoblastic leukaemia who achieved complete remission (CR), complete remission with incomplete haematological recovery (CRi) or no response.

	For Those Who Display CR	For Those Who Display CRi	For Those Who Display No Response
Benefit (%)	63	30	0
Immune (%)	14	14	14
Doom (%)	23	56	86

The probability of necessity and sufficiency provides the probability of benefit for all three subgroups of response. We assume that the 14% probability of survival for 12 months in those who displayed “no response” provides the percentage probability of being immune and is also reflected in those who displayed “complete remission” and those who displayed “complete remission with incomplete haematologic recovery.” Those who are doomed make up the remaining probabilities. Table 2 summarises the probabilities of described responses to exposure to Aucatzyl at 12 months after exposure to Aucatzyl. The values in Table 2 are derived from the probabilities of necessity and sufficiency (PNS) estimated in Table 1, together with assumptions of monotonicity. Under this assumption, PNS corresponds to the probability of benefit, while the remaining proportions are partitioned into “immune” and “doomed” categories based on observed survival in the non-responder subgroup (14% at 12 months).

4. Discussion

The FELIX study has been published to support claims of efficacy and safety for Aucatzyl in adults with relapsed/refractory acute lymphoblastic leukaemia. The study was not randomised, lacked an internal control and was not blinded [9]. Randomisation in controlled trials helps prevent systematic differences (bias) that can lead to over- or under-estimation of treatment effects, and blinding further reduces the risk of biased assessment. However, randomisation may be impractical in rare diseases, where few subjects are available and treatment options are limited, as in the FELIX study. In such settings, conventional inferential statistics may be limited in their ability to support causal conclusions [25–27].

Here, we conducted a causal analysis of the FELIX study. As external context, we refer to natural history estimates of 15% overall survival at 12 months for adults with relapsed/refractory acute lymphoblastic leukaemia [3,4]. As an internal reference, we use participants who did not respond to Aucatzyl, who exhibited an overall survival of 14% at 12 months, consistent with the natural history estimate.

There is a distinction between statistical and causal concepts: statistical concepts are defined in terms of joint distribution functions of observed static variables in order to infer associations whilst causal concepts infer associations under both static and changing

conditions (such as by an external intervention). Causal inference benefits from its own sets of mathematical and inferential tools. Whereas the typical tools of conventional statistics include such as parametric distributions, linearity, regression and hypothesis-testing, the tools of causal reasoning are model-based and make use of non-parametric statistics, directed acyclic graphs and counterfactual reasoning; the approach of causal reasoning is “data-interpreting”—where theory is brought to the data and where data are regarded as auxiliary to the interpretation of reality [11].

We have used Pearl’s box of tools [12,13] to conduct this exercise in causal reasoning; the toolbox incorporates Pearl’s “ladder of causation” where “seeing,” “doing” and “imagining” are considered as distinct activities and where each occupies its own layer in a three-layered hierarchy [14]. Thus, we have constructed a structural causal model (Tool 1) to describe the base state of adult patients with acute lymphoblastic leukaemia; the model assumes that the world is described in terms of exogenous and endogenous variables that may take various values and where the causal influence of one variable on another is represented by arrows in a directed acyclic graph and by structural equations. Note that there is not a “right choice” of a model; rather, the model is constructed to reflect our current understanding of reality.

Administration of AUCATZYL represents an external intervention (Tool 2) that enables counterfactual interpretations (Tool 3). Whilst randomised controlled trials provide information on average treatment effects by comparing outcomes after treatment [28], information on individual causal effects (PN, PS and PNS) may be obtained by combining data from different sources (here, natural history data for adults with relapsed/refractory acute lymphoblastic leukaemia and data from the FELIX study). Such observational data may encompass unobserved confounding factors and reflect individual idiosyncrasies that could be masked in a formal trial setting [29,30]. Analysis using Tool 3 suggests that participants derive the greatest benefit (expressed as the probability of necessity and sufficiency) in 12-month overall survival after exposure to AUCATZYL when they achieve complete remission (CR); benefit is less evident in those who achieve CRi and is not evident in those who do not respond (no CR/no CRi). Tool 4 suggests that the effect of AUCATZYL on overall survival is predominantly indirect via intermediary structures described in the model.

It is not yet possible to transfer learnings from the FELIX study (Tool 5) because, at this stage, it is a stand-alone study and still ongoing. In addition, too few participants had missing data to make an application of Tool 6 informative [19,20].

We evaluated whether exposure to AUCATZYL constitutes an “actual cause” of improved overall survival within the framework of Halpern and Pearl. In this analysis, the criteria for “actual cause” are satisfied in participants who achieve complete remission: (i) exposure and outcome co-occur, (ii) a counterfactual “but-for” condition is supported, in that survival would not have been expected in the absence of treatment as indicated by approximately 14–15% survival probability in non-responders and natural history cohorts, and (iii) the minimality condition is fulfilled.

The observed differences in 12-month survival between response groups (approximately 78% in complete responders versus 14% in non-responders) support this counterfactual interpretation and are consistent with the probability of necessity and sufficiency derived in Table 1. Based on this, we interpret exposure to AUCATZYL leading to complete remission as an actual cause of improved overall survival within the assumptions of the model. Analysis of “actual cause” is reinforced by considering context, normality, intention and responsibility [12]. Here, the context is adult participants in a clinical trial with relapsed/refractory B-cell acute lymphoblastic leukaemia who received AUCATZYL in a healthcare setting. Normality [22] for participants at this stage—having exhausted available treatments—would be an approximately 85% probability of death within 1 year. The

attending clinician prescribes and administers Aucatzyl with the intention of improving overall survival, while responsibility for the consequences is shared between the clinician and, after discussion of risks and benefits, the trial participant [31].

We have also demonstrated less evidence of benefit and more evidence of doom in those who do not respond to Aucatzyl versus those who do (Tool 8).

Aspects of clinical safety are, in the main, those recognised to occur following exposure to a CAR-T cell medicinal product; unknown elements of safety may yet be revealed by long-term follow-up of recipients of Aucatzyl. Similarly, durability of efficacy is an unknown that may be ascertained by long-term follow-up of recipients [9].

The limitations of this causal analysis relate to assumptions [11] about the proposed causal structure and mechanisms shown in Figure 1a,b; these assumptions may not capture the full complexity of the real world. These limitations should be interpreted in the context of causal modelling as conclusions are necessarily conditional on the assumed structure of the model. The present analysis does not seek to assert that the model fully captures the complexity of the real world. Rather the analysis provides a coherent and internally consistent framework in which the available data from the FELIX study and external natural history estimates can be interpreted.

5. Conclusions

Overall, within the assumptions of the causal model and the available data from the FELIX study, the claim that Aucatzyl is indicated for adults with relapsed/refractory B-cell precursor acute lymphoblastic leukaemia is supported by the FELIX study; the benefit–risk evaluation of Aucatzyl is favourable in the proposed indication.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/sci8070170/s1>, Supplementary Material S1: Analysis of reconstructed individual patient data from Kaplan–Meier curves; Figure S1: Kaplan–Meier plot of overall survival without censoring for stem cell transplant (FELIX study, cohort IIA, infused set); Table S1: Overall survival at 12 months: estimated probabilities (95% CI) without censoring for stem cell transplant, by best overall response (FELIX study, cohort IIA, infused set); Table S2: Differences in estimated overall survival at 12 months (95% CI) without censoring for stem cell transplant, by best overall response (FELIX study, cohort IIA, infused set). Supplementary Material S2: Toulmin argument; Figure S2: Graphical representation of the Toulmin argument structure applied to the FELIX study, showing the relationship between data, warrant and claim, together with supporting elements (backing, qualifier and rebuttal). References [32–36] are cited in the Supplementary Materials.

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Data Availability Statement: Additional data are available upon request to the authors at the following email address: essam.kerwash@mhra.gov.uk.

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