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RETRACTED: An Innovative Tool for Evidence-Based, Personalized Treatment Trials in Mucopolysaccharidosis

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Abstract: Mucopolysaccharidosis (MPS) is a group of rare metabolic diseases associated with reduced life expectancy and a substantial unmet medical need. Immunomodulatory drugs could be a relevant treatment approach for MPS patients, although they are not licensed for this population. Therefore, we aim to provide evidence justifying fast access to innovative individual treatment trials (ITTs) with immunomodulators and a high-quality evaluation of drug effects by implementing a risk–benefit model for MPS. The iterative methodology of our developed decision analysis framework (DAF) consists of the following steps: (i) a comprehensive literature analysis on promising treatment targets and immunomodulators for MPS; (ii) a quantitative risk–benefit assessment (RBA) of selected molecules; and (iii) allocation phenotypic profiles and a quantitative assessment. These steps allow for the personalized use of the model and are in accordance with expert and patient representatives. The following four promising immunomodulators were identified: adalimumab, abatacept, anakinra, and cladribine. An improvement in mobility is most likely with adalimumab, while anakinra might be the treatment of choice for patients with neurocognitive involvement. Nevertheless, a RBA should always be completed on an individual basis. Our evidence-based DAF model for ITTs directly addresses the substantial unmet medical need in MPS and characterizes a first approach toward precision medicine with immunomodulatory drugs.

Keywords: mucopolysaccharidosis; personalized medicine; individual treatment trials; immunomodulation; risk–benefit assessment; decision analysis framework

1. Introduction

Mucopolysaccharidoses (MPSs) comprise a group of 12 lysosomal storage disorders (LSDs) with no curative therapy [1,2]. All single diseases are rare or very rare, but the

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cumulative frequencies of all types account for 1 per 20,000 [2–5]. MPSs are associated with a substantial disease burden and reduced life expectancy.

At the cellular level, a genetic defect affecting the function of a lysosomal enzyme leads to an accumulation of glycosaminoglycans (GAGs) in lysosomes and the extracellular matrix (ECM). Clinically, MPS patients face a chronic and progressive impairment of multiple organ functions (skeleton, brain, heart, etc.), which is associated with severe physical disabilities and reduced life expectancy [6]. The disease spectrum is broad and ranges from mild and attenuated to severe, classical forms in each MPS type. Despite the availability of stem-cell transplantation and enzyme replacement therapy as disease-modifying therapies for some MPS types, almost all MPS patients suffer from substantial unmet medical needs. Neurocognitive, skeletal, cardiac, and respiratory involvements are the main contributors to morbidity and mortality.

Thus, therapeutic alternatives are urgently needed, and an increasingly better understanding of the underlying cell mechanism has revealed a number of potential treatment targets [7–10]. The most promising ones include the Toll-like receptor (TLR) family, most notably TLR-4, as well as the resulting transcription of pro-inflammatory proteins via NF-κB and the final activation of the NLRP3 inflammasome [7]. Despite a limited number of pre-clinical and small clinical studies, these approaches have not been clinically established so far. However, drug repurposing has emerged as a rapid and effective treatment strategy for lysosomal storage disorders and other rare diseases [11–13]. This therapeutic option to improve cellular activities and address unmet needs is highly recommended in the scientific community [14], as the translation of research results into clinical practice is generally more time-consuming in rare diseases [12,15,16]. The high interindividual heterogeneity in MPS populations adds further challenges to conventional clinical trials. Other issues include the identification of proper study endpoints and designs to suit all patients, the difficulty of including large sample sizes due to the rarity of the disease, and many others. Several experts have stated that treatment effects can only be validly assessed on an individual basis [17–19]. This demand directs us toward the use of individual treatment trials (ITTs) and N-of-1 trials, respectively.

ITTs have lower generalizability compared to conventional clinical trials, but they can overcome the above-described dilemma to some extent. In fact, ITTs are a valid and time- and cost-efficient way to close the gap between evidence and practice [20] and facilitate personalized medicine [21], which is particularly valuable for MPS and other rare diseases with high unmet clinical needs and unsatisfying treatment options. Nevertheless, the literature on ITTs for MPS is scarce. We conducted a survey on the awareness of and utilization of ITTs among MPS experts and found that most professionals knew about ITTs as an option to improve the treatability of MPS, but very few ever made use of them. The main obstacles were a lack of know-how and resources for systematic risk–benefit assessments (RBAs) of the experimental therapy and for the design and conduct of ITTs. A putative tool that facilitates systematic evidence-based RBAs was expected to overcome these barriers by the majority of MPS experts [22].

Thus, we developed an evidence-based decision model to support clinicians in their personalized decisions on the planning and conduct of ITTs with immunomodulatory drugs for their MPS patients. For that purpose, we (i) conducted a comprehensive literature review; (ii) established an expert focus group that included patient representatives; and (iii) adapted and applied the benefit and risk assessment for off-label use (BRAvO) framework to build a decision model. Decision analysis frameworks (DAFs) are semi-quantitative, structured instruments that are widely used by medical authorities for systematic RBAs. The BRAvO DAF was developed specifically for pediatric off-label use. Normally, DAFs such as BRAvO focus on the risks and benefits for an entire patient population, e.g., premature births or patients with a defined disease. In contrast, our model integrates individual patient factors into decision-making for the purpose of personalization. Thus, our model combines a comprehensive analysis of the current literature, a consensus of leading MPS experts and other specialists, and a patient perspective. Additionally, it utilizes the ap-

proved DAF methodology for semi-quantitative RBAs and can be applied in a personalized manner. We expect that the model will substantially facilitate the use of ITTs with immunomodulatory drugs to improve the treatability of MPS.

To our knowledge, this approach combining different approved methods from evidence-based medicine, qualitative research, and medical regulations has not been used before. The decision model provided in this manuscript may facilitate ITTs for MPS. Further, we describe the methodology applied for the model's development, which can be transferred to other situations with unmet clinical needs that may be addressed with ITTs.

2. Materials and Methods

2.1. Three-Step Development Process

The key feature of our model is that rational decision-making is facilitated by a quantitative RBA. The RBA is based on the following: (i) the effect sizes and probabilities of the benefits and risks, which are extracted from the literature and are based on an expert consensus; and (ii) the weighing of the risks and benefits via a patient and expert consensus.

For this purpose, in brief, the following steps were taken to develop the decision model: Firstly, a comprehensive literature review identified the most promising treatment targets (the TLR4 cascade with the NLRP3 inflammasome) [7] and immunomodulatory drugs that target these. Secondly, a quantitative RBA of the most relevant drugs was performed following the DAF methodology, which will be described in the remainder of the methods section. This step provided a quantitative risk–benefit model for four drugs. Thirdly, the quantitative risk–benefit model was applied to three different phenotypic profiles, and the probability of the most important five beneficial effects was quantitatively estimated for each single drug, which allowed for the personalized use of the model.

The model was developed by our expert board, which comprised MPS, neuroimmunology, cardiology, pharmacology, pharmacy, and biostatistics experts and patient representatives.

2.2. DAF Framing

The first step of the RBA using DAF methodology was framing the context of the disease and treatment of interest. This means defining all aspects that have to be included in the RBA. The framework BRAvO and its foundation, PrOACT-URL [23], define eight aspects that have to be considered. BRAvO further provides key questions for each aspect that assure a structured and comprehensive analysis of the benefits and risks related to efficacy, safety, and dosage [23]. We adapted these questions to fit the use of ITTs for MPS (Table 1).

Table 1. Framing in eight stages using the BRAvO framework as a template for repurposing immunomodulatory drugs in MPS.

Problem	Define the unmet medical need. Is there neurocognitive involvement? As a general rule, the decision problem is defined as whether intended off-label use is rational based on the available scientific evidence complemented with expert opinion and clinical practice, preferably in a multidisciplinary group of MPS clinicians and experts.
Alternatives	What are the alternative treatment options (label and off-label), and why are they unsuitable?
Objectives: Efficacy, Safety	What do you need to know before you can decide on the immunomodulatory drug repurposing use? The efficacy of off-label use in the intended population is established or is plausible based on extrapolation from other populations. Risks are acceptable after mitigation measures have been installed. Appropriate dosing to attain efficacy in the intended population is known. What clinical parameters and cut-offs define sufficient efficacy and unacceptable risk?

Table 1. *Cont.*

Consequences	Summary of information on what you needed to know and identification of benefits and risks.The consequences provide an explicit overview of what you need to know and specify the identified benefits and risks as a result of the objectives.
Trade Offs	Assess the balance between benefits and risks.
Uncertainty	Recognize what you do not know for sure and how it affects the benefit–risk balance. Report the uncertainty associated with the favorable and unfavorable effects. Reports on the level of evidence indicate the extent to which one can be confident that off-label use will do more good than harm. The assessment should review the quality of the studies, the consistency of the results across the studies, and the applicability to the population of interest ("directness"). Consider how the balance between favorable and unfavorable effects is affected by uncertainty. If the evidence is weak, why are the benefits and risks assumed to be acceptable for this population?
Risk Tolerance	Complement the balance with a transparent consensus and expert opinion. Judge the relative importance of the decision-maker's risk attitude for immunomodulatory drug repurposing. How does the risk tolerance of team members affect the balance?
Linked Decisions	Reflect on the impact of the decision on future decisions or on its consistency with previous decisions. The outcome of the RBA triggers subsequent decisions and recommended actions (informed consent, dissemination of knowledge).

2.3. DAF—Data Collection and Processing

The next step in the DAF-driven RBA was answering all of the key questions and analyzing all safety and efficacy data quantitatively based on a comprehensive literature analysis. Similar to meta-analyses, the process of data collection and processing must follow a detailed protocol.

Our literature analysis included all of the clinical studies and case series describing the use of one of the four immunomodulatory drugs of interest in MPS patients. Where such publications were not available, we also included clinical trials with other study populations with at least 12 weeks of treatment duration (mainly for a safety assessment).

For the documentation and analysis of the review results, we applied the method described by Nixon et al. [24], which is as follows: First, the identified and selected publications were documented in flow charts. Second, the results reported in these were retrieved in tables. Third, efficacy data was taken from one key publication per drug, which had the highest external validity. Additionally, for the safety analysis, the cumulative frequency of specific adverse effects was calculated. To achieve comparability between different publications, the specific treatment effects were rated in relation to a maximum potential effect (100%) and no effect (0%); for example, a normalization of a symptom was rated as 100% and a half-normalization as 50%. The probability of adverse events was expressed as frequency over placebo, as described by Nixon. Fourth, to allow for a comparison of the different drugs in the sense of a quantitative RBA, the effects were expressed in relation to the placebo. For example, a double frequency of the adverse effects compared to the placebo equaled a factor of 2. Equally, a factor for the intended effects was deducted from the effect sizes compared to the placebo. Thus, the risk–benefit ratio was quantified based on these factors.

The results of these calculations (Supplements S1 and S2) were used within the weighing process (see below) by our expert board.

2.4. DAF—Subjective Data and RBA

Based on comprehensive data extraction and processing, in the next step, the importance of each outcome measure was weighted. This importance rating is independent of the effect estimates. Next to the probability of an outcome, its importance needs to be considered in the decision-making process. For example, how important is it to prevent the progression of cognitive decline compared to the improvement of joint range of motion (ROM)?

Our board weighed the most relevant identified risks and benefits by importance using the visualization of a 0–100 scale, with 0 representing the conceivably least important outcome and 100 representing the most important outcome, e.g., full recovery, which is so far unrealistic. The final ratings were defined by an expert consensus.

2.5. Integration of Patient Characteristics to Allow Personalizability

To further develop the available DAF methodology toward a personalizable decision model for ITTs (Figure 1), we added two more innovative steps. Firstly, we applied our DAF to three different phenotypic profiles. The definition of the three profiles was based on the expectation that the response to a specific drug is dependent on several patient characteristics, such as main accumulated GAG, main organ involvement, severity of clinical course, putative vulnerability to specific adverse drug effects, etc. Based on general aspects, including the level of evidence, the severity and frequency of the expected adverse effects of each drug, and the above-mentioned patient characteristics, the first and second drug choices were defined for each phenotypic profile. To allow for an even more personalized use of the decision model, the probability of the five most important beneficial effects was quantitatively estimated for each single drug. With that, the leading organ manifestation of each individual patient was taken into account.

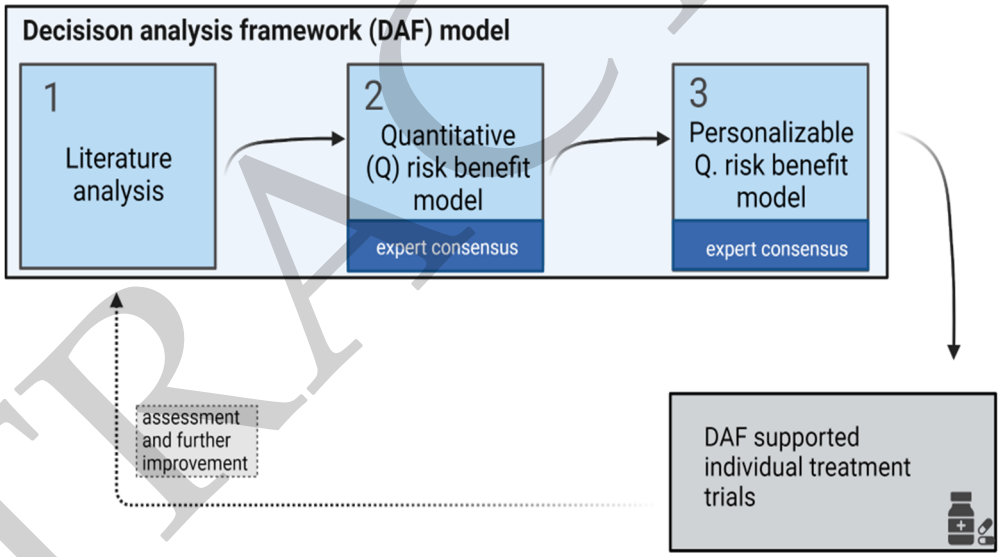

Figure 1. Iterative process of our DAF model development. The literature research laid the foundation for the subsequent personalizable quantitative risk–benefit model, which is based on expert and patient consensus and finally led to DAF-supported ITTs. The DAF model will be assessed and further improved by new publications, ITT results, and patient opinions.

3. Results

Our DAF model was implemented in several steps, and each achievement with our expert panel and patient representatives was described in detail.

3.1. Beneficial and Adverse Effects of the Most Relevant Immunomodulatory Drugs

A comprehensive literature review on the inflammation-driven cell pathology in MPS [7] identified two main targets for intervening in the viscous circle of inflammation in MPS, namely (i) the TLR4 receptor and cytokine/chemokine upregulation and (ii) the activation of the inflammasome NLRP3. This led us to the following nine promising molecules: adalimumab, anakinra, alemtuzumab, pentosan poylsulfat (PPS), ataluren, genistein, cladribine, and odiparcil.

Afterward, a database search using Medline and others (ClinicalTrials, Clarivate, and SpringerLink) was performed for each drug using the same search strategy with a defined

strict procedure. We searched for English-language reports of (i) studies on MPS (regardless of the study type and design), (ii) MPS case reports, and (iii) phase III or IV randomized placebo-controlled pediatric clinical trials with at least 12 weeks of treatment duration. This led us to exclude four drugs (ataluren, genistein, odiparcil, and PPS) due to (i) an unexplained mechanism of action and (ii) a low level of evidence compared to the other molecules. Genistein was excluded despite a relatively high number of published studies (324 reports) due to its repeatedly reported low efficacy, even in higher doses [25,26].

Consequently, the remaining five molecules (alemtuzumab, anakinra, adalimumab, abatacept, and cladribine) were further assessed using a structured, quantitative RBA, which is also used by regulatory authorities [27,28]. The results of this assessment led the expert board to exclude alemtuzumab due to safety issues [29–48].

Consequently, the four top candidates were identified from 18 selected publications out of 2270 publications (Supplement S1). Three (adalimumab, abatacept, and anakinra) of the four immunomodulatory drugs had already been clinically studied in MPS [49–51]; NCT01917708. Oral cladribine, an immunodepleting agent approved for the treatment of multiple sclerosis (MS), was also considered due to its non-invasive application and its overall good risk–benefit profile among MS patients [52]. Moreover, as a small molecule, it can cross the blood–brain barrier to reach the tissues of interest in MPS patients with CNS involvement [53]. Lastly, short-therapy cycles induce long-lasting anti-inflammatory effects, making it a convenient treatment option [54,55].

To gain an overview of the potential benefits and risks of each drug, the external validity of the reported safety and efficacy data was classified (clinical vs. pre-clinical and by study population) and taken into account with the spectrum and frequency of adverse effects and the delivery route (Table 2).

Table 2. Comparison of the level of evidence available and key characteristics of the immunomodulatory drugs of interest (blank means no data or no data available). * evidence of increased risk, especially leukemia and lymphoma; ** in combination with HSCT (hematopoietic stem-cell transplantation) in children with MPS and other non-malignant diseases.

Drug	PRO				CON					
	MPS Clinical Data	MPS Pre-Clinical Data	Pediatric Data beyond MPS	Malignancy *	Infection	Low CNS Bioavailability	Renal Impair-ment	Hepatic Impair-ment	Cardiac Involve-ment	Invasive
adalimumab	X MPS I $n = 1$, MPS II $n = 1$		X	X	X 3.2/100 PY	X			X	X (sc)
abatacept	X MPS I **		X	X	X 1.3/100 PY	X				X (iv/sc)
anakinra	X MPS III $n = 7$		X		X 5.4/100 PY	X	X			X (sc)
cladribine			X	(X)	X 0.9/100 PY		X	X	X	

3.2. Drug Selection for Defined Phenotypic Groups

To enable the identification of the best candidate drug for specific patients, firstly, three phenotypic groups were built. These groups took into account that the CNS and bones are particularly hard to reach as targets and that accumulation of heparan sulfate (HS) induces inflammation mainly via the TLR-4 response, whereas dermatan sulfate (DS), keratan sulfate (KS), and chondroitin sulfate (CS) mainly act via other cascades [7]. Consequently, phenotypic group one was characterized by an HS-accumulation-induced CNS pathology, such as in MPS types I, II, III, and VII. Phenotypic group two was characterized by HS-induced effects outside of the brain, such as in the attenuated forms of MPS I and MPS II. Phenotypic group three included MPS forms that showed DS-, KS-, and/or CS-accumulation-induced inflammation, such as in MPS IV and MPS VI (Figure 2).

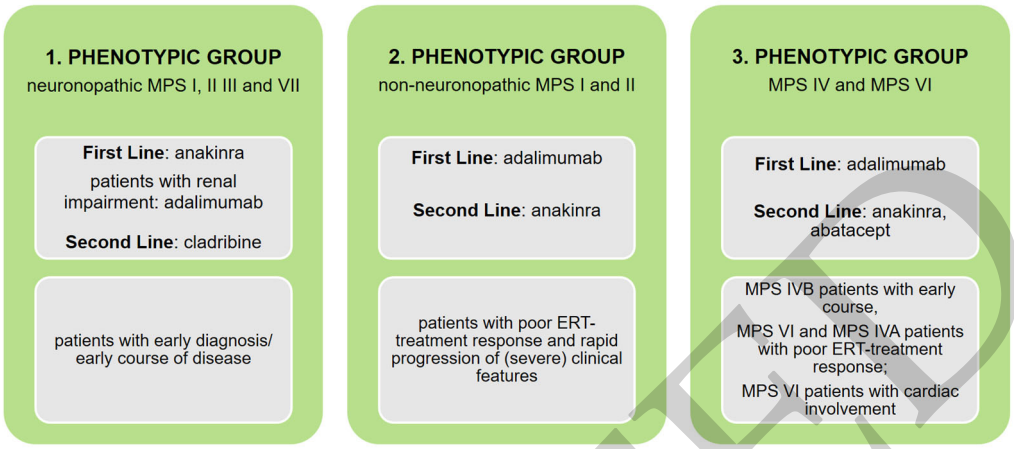

Figure 2. Assessment of concordances between the identified immunomodulators and various MPS patient profiles, structured according to CNS involvement, with further clarification regarding MPS type, onset of the disease, organ involvement, diagnosis, etc.

For each group, our expert board defined a first- and second-choice molecule.

For example, in neuronopathic patients with HS accumulation, anakinra was favored over adalimumab due to its proven CNS effects, despite higher infection rates. Furthermore, increasing evidence in support of a causative relationship between chronic inflammation and CNS-related disorders emphasizes the potential for targeting the IL-1β (interleukin-1β) pathways in the brain with anakinra as a promising strategy [56,57]. Cladribine had not been studied for MPS patients. Nevertheless, it was chosen as the second-choice drug for neuronopathic MPS patients because of the above-mentioned reasons and because it additionally targets the inflammasome NLRP3 [58].

Adalimumab, a TNF-α (tumor necrosis factor-α) inhibitor, was favored for the second and third phenotypic groups without CNS involvement, as TNF-α is associated with pain and physical disabilities despite treatment with ERT (enzyme replacement therapy) and/or HSCT (hematopoietic stem-cell transplantation) [59]. Moreover, animal models and case reports of MPS have revealed joint abnormalities similar to those seen in inflammatory joint disease and improvements in inflammation, joint pathology, and physical function when treated with TNF-α inhibition [60–62].

3.3. Value Tree

In addition to the BRAvO methodology and in line with the BRAT framework [63], we generated a value tree of the most important treatment effects. This step primarily served as a visualization of the identified key benefits and risks and provided a precise definition of each efficacy and safety outcome and a measurement scale, respectively.

The core idea of developing a value tree was to find simplicity and structure by defining and organizing the most important benefits and risks, which are driving the benefit–risk balance [24]. Our value tree (Figure 3) lists the most important five potential risks and benefits of the selected immunomodulatory candidates. These risks and benefits are substantiated and further characterized for each candidate by the published evidence (e.g., seriousness, frequency, preventability, and reversibility of adverse events) and by an expert and patient representative consensus (e.g., probability and effect size of the potential benefits).

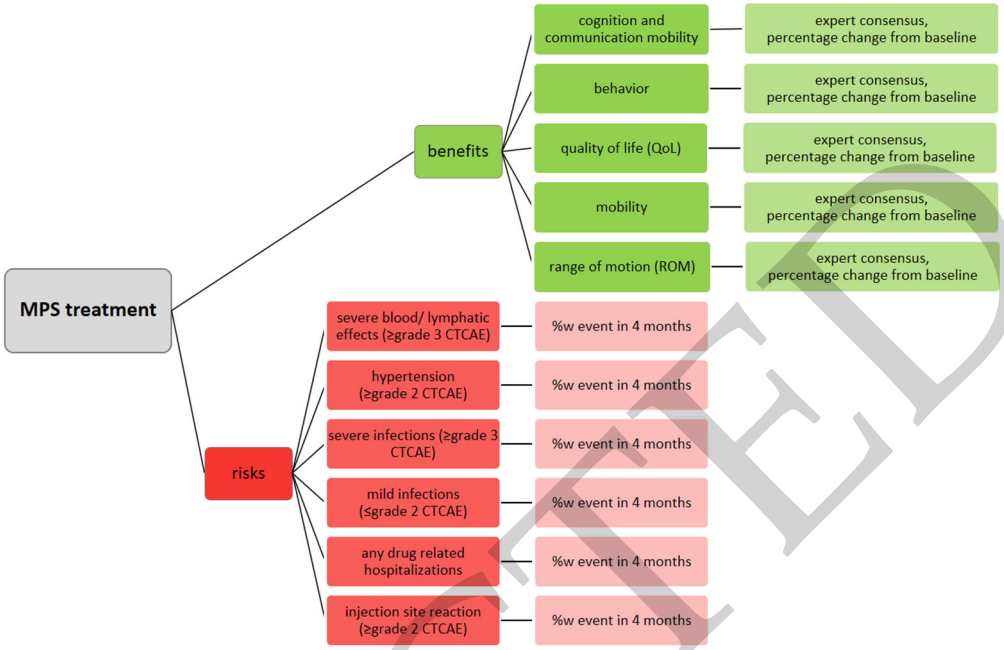

Figure 3. Our value tree for MPS treatment consists of five potential benefits (marked in green) and five potential risks (marked in red), with the associated measured scales behind; CTCAE = common terminology criteria for adverse events.

For the adverse events, the common terminology criteria for adverse events (CTCAE) were utilized, and the expected occurrence rate (%) during a fictitious ITT of 4 months was provided.

3.4. Weighing Potential Risks and Benefits

For personalized, informed, and rational decision-making in the sense of evidence-based practice, the probability and effect size of the intended and adverse treatment effects have to be weighed, taking the medical condition, personal situation, and values into consideration. For example, improvement in communication and behavior may be of the highest importance in a severely affected neuronopathic patient, whereas improvement in joint flexibility may be more important in a mildly cognitively impaired patient. Thus, to include the individual patient situation in our decision tool, we weighed the importance of the intended and adverse effects using expert and patient consensus. This was implemented as a two-step approach. Firstly, the rating of the potential benefits and risks was completed separately. Secondly, the weighing of the most important intended and adverse treatment effects was completed.

For this purpose, we used a scale from 0 (lowest importance) to 100 (highest importance). For example, the rare adverse reaction of a "severe blood and lymphatic event" with some immunomodulators was defined as the worst possible scenario, while an improvement in cognition and communication was defined as the putative effect (Figure 4). By using this quasi-quantitative approach, the relative importance of both intended and adverse effects could be judged.

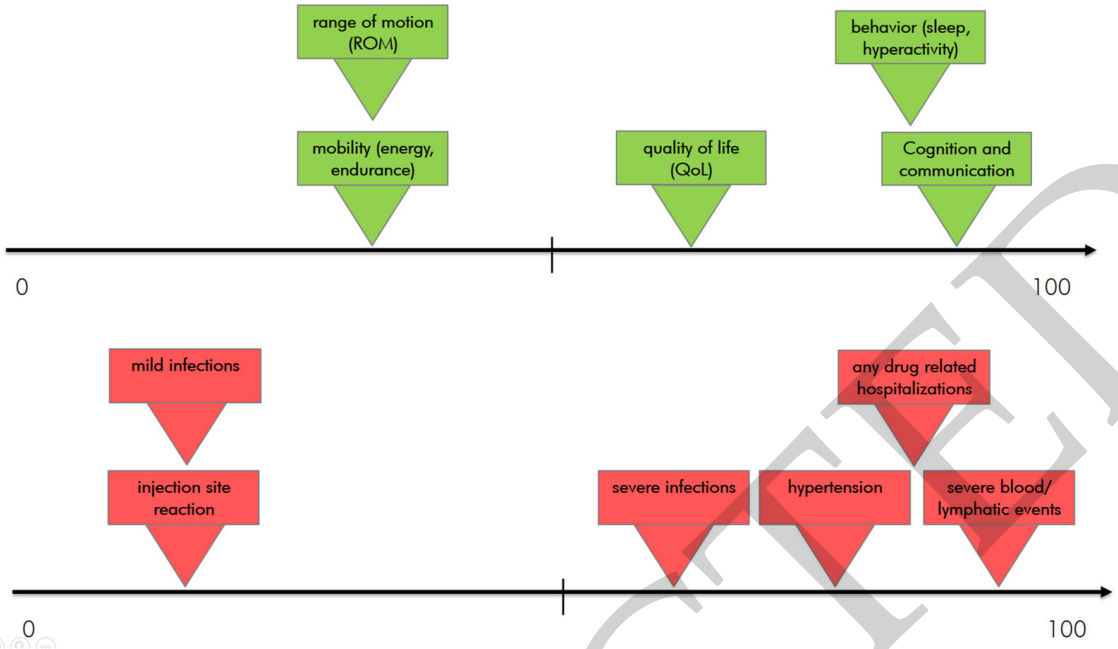

Figure 4. Weighing of potential benefits (green items) and risks (red items) on a number scale via expert and patient consensus (demonstrated with examples of neuronopathic MPS I, II, III, or VII patients).

Finally, the best-case scenario, improvement in cognition and communication, and the worst-case scenario, severe blood and lymphatic events, were compared with each other. Overall, five MPS patients or parents participated and made an assessment by defining percentages for both outcomes, with the following mean results:

- Best-case scenario: 60%
- Worst-case scenario: 40%

For now, this evaluation of the importance of single effects is provided in a sentinel manner, but at the next level, the tool will allow for weighing by the individual patients/parents that consider an ITT.

3.5. Assessing the Chance of Improvement

The efficacy of our top immunomodulatory drugs was evaluated according to the identified beneficial outcomes—mobility, quality of life (QoL), behavior, cognition, communication, and, lastly, range of motion (ROM). The mean percentage chance of improvement was calculated for all four drugs, which resulted from literature research, relevant efficacy trials, expert consensus, and personal assessment (Table 3). Overall, an improvement in mobility and ROM was most likely with adalimumab, abatacept, and cladribine as therapy, while anakinra or cladribine were the treatment choices for cognition, communication, behavior, and QoL.

Overall, our decision framework comprises the best available evidence on immunomodulation in MPS patients, as appraised by experts and patients/representatives. It takes into consideration the importance and probability of intended and adverse effects and, thus, provides an ideal foundation for an evidence-based, personalized decision-making process with regard to ITTs. These advantages of the DAF are summarized in Table 4.

Table 3. Probability of the most important beneficial outcomes (QoL, behavior, cognition, communication, and ROM) using literature research, clinical trials (MPS and beyond), expert consensus, and patient assessments.

		Mobility	QoL	Behavior	Cogn/Comm	ROM
Value of Importance		**33%**	66%	80%	90%	33%
Chance of Improvement						
Anakinra						
Drug	Expert consensus	5%	80%	80%	40%	5%
	Polgreen 2022, NCT04018755		60%	60%	60%	
	Schnaberg 2020, NCT03265132	90%	90%			70%
	mean	48%	77%	70%	50%	38%
Placebo	Polgreen 2022, NCT04018755	20%	5%	5%	5%	
	Schnaberg 2020, NCT03265132	20%	20%			20%
	mean	20%	13%	5%	5%	20%
Adalimumab						
Drug	Expert consensus	80%	40%	20%	20%	80%
	Polgreen 2017, PMID: 28119823	40%	30%	50%		90%
	Burgos-Vargas 2015, PMID: 26223543, NCT01166282	70%	90%			
	mean	63%	53%	35%	20%	85%
Placebo	Polgreen 2017, PMID: 28119823	5%	5%	5%	5%	20%
	Burgos-Vargas 2015, PMID: 26223543, NCT01166282	40%	40%			
	mean	23%	23%	5%	5%	20%
Abatacept						
Drug	Expert consensus	60%	60%	5%	5%	60%
	Ruperto 2008, PMID: 18632147, PMID: 20597110, NCT00095173	60%	40%			50%
	Lovell 2015, PMID: 26097215	80%		5%	5%	
	mean	67%	50%	5%	5%	55%
Placebo	Ruperto 2008, PMID: 18632147, PMID: 20597110, NCT00095173	20%	20%			20%
	Lovell 2015, PMID: 26097215	20%		5%	5%	
	mean	20%	20%	5%	5%	20%
Cladribine						
Drug	Expert consensus	60%	60%	60%	40%	60%
	Dhall 2008, PMID: 17455311	90%		70%	70%	90%
	Stine 2004, PMID: 15170896	90%		90%	90%	90%
	Giovannoni 2010, PMID: 20089960	30%	80%	80%	80%	30%
	mean	68%	70%	75%	70%	68%
Placebo	Giovannoni 2010, PMID: 20089960	20%	20%	5%	5%	20%
	mean	20%	20%	5%	5%	20%

Table 4. Comparison of the important steps in the decision-making process and conduct of ITTs with and without DAF [64]; three key steps for DAF-based ITT: literature research (^{L}), expert consensus (^{E}), and patient perspective (^{P}).

	ITT without DAF	DAF-Based ITT
		pre-appraised from 2270 publications ^{L} by expert ^{E} and patient/parent ^{P} consensus
Identification of best drugs	from primary literature	4 top candidates identified from 18 selected publications out of 2270 ^{L} by expert consensus ^{E}
Assessment of putative beneficial and adverse treatment effects	from primary literature	quantitatively pre-appraised for all candidates ^{L,E}

Table 4. *Cont.*

	ITT without DAF	DAF-Based ITT
Estimation of putative effect size and probability	from primary literature	quasi-quantitative consensus [L,E] for 3 phenotypic groups
Identification of patient factors, which predispose for beneficial/adverse response	single expert opinion	quasi-quantitative consensus [L,E] for 3 phenotypic groups
Discussion with peer and/or interdisciplinary/interprofessional experts (e.g., scientist, pharmacist etc.)	dependent on personal network	expert consensus for all assessments [L,E]
Assessment of patient/parent values	individual	sentinel [P] plus individual patient perspective
Weighing of pros and cons	based on clinical experience	expert and sentinel patient consensus [E,P]
Informed consent/board and/or payers approval	individual preparation	use of prepared literature appraisal for justification
Treatment and assessment plan	based on clinical experience	expert and sentinel patient consensus [E,P] to be individualized
Learning from ITT experience	single center experience possibly publication of case report	integration into and availability to public by DAF and mutual publications

4. Discussion

Systematic integration of bioinformatics into clinical decision-making has previously been established to facilitate personalized patient care [65]. We developed a strategy by modifying the DAF methodology, which is broadly used by medical agencies [66], and combining it with an evidence-based, patient-centered expert consensus process. Therewith, we identified first- and second-line drugs, including anakinra, cladribine, abatacept, and adalimumab, for three defined phenotypic groups that facilitate decision-making with respect to ITTs. Moreover, our innovative approach may be applied to other rare diseases and repurposing candidates.

Despite seven market-approved medicines for the treatment of MPS, the majority of patients suffer from a substantial burden of disease and reduced life expectancy. Therefore, additional treatment approaches are urgently needed. Key drivers of chronical progression, even in ERT-treated patients, are GAG-storage-induced inflammatory processes [7]. This renders immunomodulation a promising alternative or supportive therapy option [7]. However, clinical drug development is particularly time-consuming for rare diseases such as MPS [15,67]. As many immunomodulatory drugs are market-approved for other indications, ITTs combined with these are an obvious and time-efficient option to improve the treatability of MPS [20,21]. Drug repurposing is an EMA-recommended [27], highly personalizable [68] option to improve treatability in rare disorders [11–13], which is still underutilized, and only a few MPS centers make use of this, as shown by us previously [22].

Key hurdles, expressed by experts in our survey, included time and other efforts needed to plan and conduct the trials, as well as a lack of training in ITTs [22]. This is in line with other work that has shown that the know-how and efforts associated with profound RBAs needed to justify and plan ITTs are also key barriers in other fields [69].

For evidence-based RBAs, medical agencies have been using the DAF as the gold standard methodology for many years [66]. Recently, the BRAvO framework [23], which is founded on established DAFs [70], has been developed for off-label use in children. To facilitate personalized decisions for ITTs in MPS, we added a patient-centered expert consensus process to define archetypic phenotype groups and prioritize candidate immunomodulatory drugs for each group. This prioritization process included a quantitative weighing of potential benefits and risks and the external validity of the underlying evidence. The defined phenotypic groups differed in their main symptoms (CNS vs. tendon and bone pathology) and the inflammatory pathways involved (IL-1β vs. TNF-α). Therefore, the bioavailability of the immunomodulatory drugs and the mode of action both need to be taken into consideration. The quantitative assessment of the importance of specific potential treatment effects and the probability of adverse and intended effects allowed for personalized decisions beyond the three phenotypic groups based on the individual symptoms, needs, and values of patients interested in an ITT. Thus, our model provides an expert-appraised, patient-centered overview of the current evidence on the most relevant

four immunomodulatory drugs for ITTs in MPS, namely anakinra, cladribine, abatacept, and adalimumab. In addition to a literature review [7], it also includes a DAF-based quantitative RBA that consists of a patient-centered weighing of risk–benefit profiles. The model can, therefore, substantially reduce the efforts involved in clinical decision-making in favor of or against an ITT in MPS. Moreover, the patient-centered expert consensus provides a valuable foundation for the justification of drug repurposing toward payers or other relevant stakeholders. Additionally, our board defined a standard for a treatment assessment and a template for informed consents to adapt to the local situation of the respective centers. In comparison to the standard situation before a potential ITT, our work can save clinicians significant time and effort. It provides a high level of evidence and quality to secure a good decision, including the option to personalize a decision toward a specific patient (Table 4).

Areas of limitation in our RBA approach include the non-consideration of MPS X [1] and MPS plus syndrome [71], which have recently been identified, as well as MPS IX [72], with only four cases reported so far. Furthermore, exceptions have to be made for potential patients for gene therapy, which is considered more promising. As minimum criteria, we defined available (pre-) clinical data in MPS or clinical data in pediatric populations; therefore, we may have missed potential molecules that do not fulfill our criteria for integration in this model. However, this is a necessary concession to safety evidence.

The model and associated documents will be provided to interested MPS centers and are expected to increase the quality and utilization of ITTs with immunomodulatory drugs in MPS. The results of the ITTs should be fed back into our model as an important current source of evidence. Thus, the model is not intended to be fully finished yet but rather subject to work in progress, and future versions and modifications will be provided to expert centers continuously.

5. Conclusions

This is the first evidence-based, personalizable, quantitative DAF model for MPS professionals, which provides a transparent, rational, and consistent approach to RBAs and communication of treatment (side) effects and immunomodulatory drug selection in order to enhance the frequency and possibility of ITT implementation in MPS. The adaptation of a validated framework, an international and interdisciplinary expert panel, and systematic literature research laid the foundations for evidence-based ITTs using immunomodulatory drugs.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/pharmaceutics15051565/s1, The data that support the findings of this study are available as Supplementary Information S1 and S2.

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References

1. Verheyen, S.; Blatterer, J.; Speicher, M.R.; Bhavani, G.S.; Boons, G.J.; Ilse, M.B.; Andrae, D.; Sproß, J.; Vaz, F.M.; Kircher, S.G.; et al. Novel subtype of mucopolysaccharidosis caused by arylsulfatase K (ARSK) deficiency. *J. Med. Genet.* **2022**, *59*, 957–964. [CrossRef] [PubMed]
2. Çelik, B.; Tomatsu, S.C.; Tomatsu, S.; Khan, S.A. Epidemiology of Mucopolysaccharidoses Update. *Diagnostics* **2021**, *11*, 273. [CrossRef] [PubMed]
3. Meikle, P.J.; Hopwood, J.J.; Clague, A.E.; Carey, W.F. Prevalence of lysosomal storage disorders. *JAMA* **1999**, *281*, 249–254. [CrossRef] [PubMed]
4. Caruso, R.C.; Kaiser-Kupfer, M.I.; Muenzer, J.; Ludwig, I.H.; Zasloff, M.A.; Mercer, P.A. Electroretinographic findings in the mucopolysaccharidoses. *Ophthalmology* **1986**, *93*, 1612–1616. [CrossRef]
5. Poorthuis, B.J.; Wevers, R.A.; Kleijer, W.J.; Groener, J.E.; de Jong, J.G.; van Weely, S.; Niezen-Koning, K.E.; van Diggelen, O.P. The frequency of lysosomal storage diseases in The Netherlands. *Hum. Genet.* **1999**, *105*, 151–156. [CrossRef]
6. Muenzer, J. Mucopolysaccharidoses. *Adv. Pediatr.* **1986**, *33*, 269–302.
7. Wiesinger, A.-M.; Bigger, B.; Giugliani, R.; Scarpa, M.; Moser, T.; Lampe, C.; Kampmann, C.; Lagler, F.B. The Inflammation in the Cytopathology of Patients with Mucopolysaccharidoses-Immunomodulatory Drugs as an Approach to Therapy. *Front. Pharmacol.* **2022**, *13*, 863667. [CrossRef]
8. Archewith, D.; Langford-Smith, K.J.; Bigger, B.W.; Fildes, J.E. Mucopolysaccharide diseases: A complex interplay between neuroinflammation, microglial activation and adaptive immunity. *J. Inherit. Metab. Dis.* **2014**, *37*, 1–12. [CrossRef]
9. Parker, H.; Bigger, B.W. The role of innate immunity in mucopolysaccharide diseases. *J. Neurochem.* **2019**, *148*, 639–651. [CrossRef]
10. Mandolfo, O.; Parker, H.; Bigger, B. Innate Immunity in Mucopolysaccharide Diseases. *Int. J. Mol. Sci.* **2022**, *23*, 1999. [CrossRef]
11. Monticelli, M.; Liguori, L.; Allocca, M.; Bosso, A.; Andreotti, G.; Lukas, J.; Monti, M.C.; Morretta, E.; Cubellis, M.V.; Mele, B.H. Drug Repositioning for Fabry Disease: Acetylsalicylic Acid Potentiates the Stabilization of Lysosomal Alpha-Galactosidase by Pharmacological Chaperones. *Int. J. Mol. Sci.* **2022**, *23*, 5105. [CrossRef] [PubMed]
12. Sun, W.; Zheng, W.; Simeonov, A. Drug discovery and development for rare genetic disorders. *Am. J. Med. Genet. A* **2017**, *173*, 2307–2322. [CrossRef] [PubMed]
13. Monticelli, M.; Mele, B.H.; Allocca, M.; Liguori, L.; Lukas, J.; Monti, M.C.; Morretta, E.; Cubellis, M.V.; Andreotti, G. Curcumin Has Beneficial Effects on Lysosomal Alpha-Galactosidase: Potential Implications for the Cure of Fabry Disease. *Int. J. Mol. Sci.* **2023**, *24*, 1095. [CrossRef]
14. Pushpakom, S.; Iorio, F.; Eyers, P.A.; Escott, K.J.; Hopper, S.; Wells, A.; Doig, A.; Guilliams, T.; Latimer, J.; McNamee, C.; et al. Drug repurposing: Progress, challenges and recommendations. *Nat. Rev. Drug Discov.* **2019**, *18*, 41–58. [CrossRef]
15. Platt, F.M. Emptying the stores: Lysosomal diseases and therapeutic strategies. *Nat. Rev. Drug Discov.* **2018**, *17*, 133–150. [CrossRef]
16. Heemstra, H.E.; van Weely, S.; Büller, H.A.; Leufkens, H.G.; de Vrueh, R.L. Translation of rare disease research into orphan drug development: Disease matters. *Drug Discov. Today* **2009**, *14*, 1166–1173. [CrossRef]
17. Kakkis, E.D. Enzyme replacement therapy for the mucopolysaccharide storage disorders. *Expert Opin. Investig. Drugs* **2002**, *11*, 675–685. [CrossRef]
18. Muenzer, J.; Wraith, J.E.; Clarke, L.A. Mucopolysaccharidosis I: Management and treatment guidelines. *Pediatrics* **2009**, *123*, 19–29. [CrossRef]
19. Fung, A.; Yue, X.; Wigle, P.R.; Guo, J.J. Off-label medication use in rare pediatric diseases in the United States. *Intractable Rare Dis. Res.* **2021**, *10*, 238–245. [CrossRef]
20. Vohra, S.; Shamseer, L.; Sampson, M.; Bukutu, C.; Schmid, C.H.; Tate, R.; Nikles, J.; Zucker, D.R.; Kravitz, R.; Guyatt, G.; et al. CONSORT extension for reporting N-of-1 trials (CENT) 2015 Statement. *BMJ* **2015**, *350*, h1738. [CrossRef] [PubMed]
21. Wolters, T.L.C.; Van Vlijmen, J. N-of-1 trials: The one and only. *Ned. Tijdschr. Geneeskd.* **2021**, *165*, D6149. [PubMed]
22. Wiesinger, A.M.; Strobl, H.; Lagler, F.B. Individual Treatment Trials-Do Experts Know and Use This Option to Improve the Treatability of Mucopolysaccharidosis? *Pharmaceuticals* **2023**, *16*, 416. [CrossRef] [PubMed]
23. van der Zanden, T.M.; Mooij, M.G.; Vet, N.J.; Neubert, A.; Rascher, W.; Lagler, F.B.; Male, C.; Grytli, H.; Halvorsen, T.; de Hoog, M.; et al. Benefit-Risk Assessment of Off-Label Drug Use in Children: The Bravo Framework. *Clin. Pharmacol. Ther.* **2021**, *110*, 952–965. [CrossRef]
24. Nixon, R.; Dierig, C.; Mt-Isa, S.; Stöckert, I.; Tong, T.; Kuhls, S.; Hodgson, G.; Pears, J.; Waddingham, E.; Hockley, K.; et al. A case study using the PrOACT-URL and BRAT frameworks for structured benefit risk assessment. *Biom. J.* **2016**, *58*, 8–27. [CrossRef]
25. de Ruijter, J.; Valstar, M.J.; Narajczyk, M.; Wegrzyn, G.; Kulik, W.; Ijlst, L.; Wagemans, T.; van der Wal, W.M.; Wijburg, F.A. Genistein in Sanfilippo disease: A randomized controlled crossover trial. *Ann. Neurol.* **2012**, *71*, 110–120. [CrossRef] [PubMed]
26. Ghosh, A.; Rust, S.; Langford-Smith, K.; Weisberg, D.; Canal, M.; Breen, C.; Hepburn, M.; Tylee, K.; Vaz, F.M.; Vail, A.; et al. High dose genistein in Sanfilippo syndrome: A randomised controlled trial. *J. Inherit. Metab. Dis.* **2021**, *44*, 1248–1262. [CrossRef] [PubMed]
27. EMA. *Proposal for a Framework to Support Not-For-Profit Organisations and Academia (Institutions and Individuals) in Drug Repurposing*; European Medicines Agency—EMA: Amsterdam, The Netherlands, 2019; p. 12.
28. EMA. *Benefit-Risk Methodology Project*; Work Package 3 Report: Field Tests; European Medicines Agency—EMA: Amsterdam, The Netherlands, 2011.

29. Meunier, B.; Rico, A.; Seguier, J.; Boutiere, C.; Ebbo, M.; Harle, J.R.; Schleinitz, N.; Pelletier, J. Life-threatening autoimmune warm hemolytic anemia following treatment for multiple sclerosis with alemtuzumab. *Mult. Scler.* **2018**, *24*, 811–813. [CrossRef] [PubMed]
30. di Ioia, M.; Farina, D.; di Tommaso, V.; Travaglini, D.; Pietrolongo, E.; Onofrj, M.; de Luca, G. Simultaneous early-onset severe autoimmune hemolytic anemia and albuminuria during alemtuzumab treatment for multiple sclerosis. *Mult. Scler.* **2018**, *24*, 813–815. [CrossRef]
31. Ferraro, D.; Camera, V.; Vitetta, F.; Zennaro, M.; Ciolli, L.; Nichelli, P.F.; Sola, P. Acute coronary syndrome associated with alemtuzumab infusion in multiple sclerosis. *Neurology* **2018**, *90*, 852–854. [CrossRef]
32. Liou, A.A.; Skiver, B.M.; Yates, E.; Persad, P.; Meyer, D.; Farland, A.M.; Rocco, M.V. Acute Thrombotic Microangiopathy and Cortical Necrosis Following Administration of Alemtuzumab: A Case Report. *Am. J. Kidney Dis.* **2019**, *73*, 615–619. [CrossRef]
33. Whiteside, D.; Barth, S.; Datta, A.; Trip, S.A. Pneumonitis secondary to alemtuzumab in a patient with multiple sclerosis—A non-infectious cause of breathlessness. *Mult. Scler. Relat. Disord.* **2018**, *22*, 139–140. [CrossRef] [PubMed]
34. El Sankari, S.; Dahlqvist, G.; Monino, L.; van Pesch, V. Auto-immune hepatitis in a patient with multiple sclerosis treated with alemtuzumab. *Acta Neurol. Belg.* **2018**, *118*, 331–333. [CrossRef] [PubMed]
35. Giarola, B.; Massey, J.; Barnett, Y.; Rodrigues, M.; Sutton, I. Autoimmune encephalitis following alemtuzumab treatment of multiple sclerosis. *Mult. Scler. Relat. Disord.* **2019**, *28*, 31–33. [CrossRef]
36. Midaglia, L.; Gratacòs, M.; Caronna, E.; Raguer, N.; Sastre-Garriga, J.; Montalban, X.; Tintoré, M. Myasthenia gravis following alemtuzumab therapy for multiple sclerosis. *Neurology* **2018**, *91*, 622–624. [CrossRef] [PubMed]
37. Yiannopoulou, K.G.; Papadimitriou, D.; Anastasiou, A.I.; Siakantaris, M. Neutropenia with fatal outcome in a multiple sclerosis patient 23 days after alemtuzumab infusion. *Mult. Scler. Relat. Disord.* **2018**, *23*, 15–16. [CrossRef] [PubMed]
38. Hoffman, B.M.; Zeid, N.A.; Alam, U.; Caress, J.B. Lambert-Eaton myasthenic syndrome associated with alemtuzumab administration. *Mult. Scler. Relat. Disord.* **2019**, *27*, 131–132. [CrossRef] [PubMed]
39. Lapucci, C.; Gualandi, F.; Mikulska, M.; Palmeri, S.; Mancardi, G.; Uccelli, A.; Laroni, A. Serum sickness (Like Reaction) in a patient treated with alemtuzumab for multiple sclerosis: A case report. *Mult. Scler. Relat. Disord.* **2018**, *26*, 52–54. [CrossRef] [PubMed]
40. Graf, J.; Ringelstein, M.; Lepka, K.; Schaller, J.; Quack, H.; Hartung, H.P.; Aktas, O.; Albrecht, P. Acute sarcoidosis in a multiple sclerosis patient after alemtuzumab treatment. *Mult. Scler.* **2018**, *24*, 1776–1778. [CrossRef]
41. Willis, M.D.; Hope-Gill, B.; Flood-Page, P.; Joseph, F.; Needham, E.; Jones, J.; Coles, A.; Robertson, N.P. Sarcoidosis following alemtuzumab treatment for multiple sclerosis. *Mult. Scler.* **2018**, *24*, 1779–1782. [CrossRef]
42. Ruck, T.; Pfeuffer, S.; Schulte-Mecklenbeck, A.; Gross, C.C.; Lindner, M.; Metze, D.; Ehrchen, J.; Sondermann, W.; Pul, R.; Kleinschnitz, C.; et al. Vitiligo after alemtuzumab treatment: Secondary autoimmunity is not all about B cells. *Neurology* **2018**, *91*, e2233–e2237. [CrossRef]
43. Alcalá, C.; Pzére-Miralles, F.; Gascón, F.; Evole, M.; Estutia, M.; Gil-Perotín, S.; Casanova, B. Recurrent and universal alopecia areata following alemtuzumab treatment in multiple sclerosis: A secondary autoimmune disease. *Mult. Scler. Relat. Disord.* **2019**, *27*, 406–408. [CrossRef] [PubMed]
44. Myro, A.Z.; Bjerke, G.; Zarnovicky, S.; Holmøy, T. Diffuse alveolar hemorrhage during alemtuzumab infusion in a patient with multiple sclerosis: A case report. *BMC Pharmacol. Toxicol.* **2018**, *19*, 75. [CrossRef]
45. Pisa, M.; Della Valle, P.; Coluccia, A.; Martinelli, V.; Comi, G.; D'Angelo, A.; Moiola, L. Acquired haemophilia A as a secondary autoimmune disease after alemtuzumab treatment in multiple sclerosis: A case report. *Mult. Scler. Relat. Disord.* **2019**, *27*, 403–405. [CrossRef] [PubMed]
46. Aouad, P.; Yiannikas, C.; Fernando, S.L.; Parratt, J. A case of autoimmune myositis after treatment with alemtuzumab for multiple sclerosis. *Mult. Scler. J. Exp. Transl. Clin.* **2018**, *4*, 2055217318819012. [CrossRef] [PubMed]
47. Richter, S.; Wagner, B.; Celius, E.G. Two cases of diabetes mellitus type 1 after alemtuzumab treatment for multiple sclerosis: Another probable secondary autoimmune disease. *J. Neurol.* **2019**, *266*, 1270–1271. [CrossRef]
48. Gerevini, S.; Capra, R.; Bertoli, D.; Sottini, A.; Imberti, L. Immune profiling of a patient with alemtuzumab-associated progressive multifocal leukoencephalopathy. *Mult. Scler.* **2019**, *25*, 1196–1201. [CrossRef]
49. Polgreen, L.E.; Kunin-Batson, A.; Rudser, K.; Vehe, R.K.; Utz, J.J.; Whitley, C.B.; Dickson, P. Pilot study of the safety and effect of adalimumab on pain, physical function, and musculoskeletal disease in mucopolysaccharidosis types I and II. *Mol. Genet. Metab. Rep.* **2017**, *10*, 75–80. [CrossRef]
50. Polgreen, L.; Chen, A.; O'Neill, C.; Luzzi, A.; Iacovino, M.; Eisengart, J. Open-label clinical trial of anakinra in mucopolysaccharidosis type III: Interim analysis. *Mol. Genet. Metab.* **2020**, *132*, S87–S88. [CrossRef]
51. Polgreen, L.; O'Neill, C.; Chen, A.; Eisengart, J. Phase I/II clinical trial of anakinra in Sanfilippo syndrome: Outcomes from 8 weeks of palliative treatment. *Mol. Genet. Metab.* **2022**, *135*, S100. [CrossRef]
52. Moser, T.; Ziemssen, T.; Sellner, J. Real-world evidence for cladribine tablets in multiple sclerosis: Further insights into efficacy and safety. *Wien Med. Wochenschr.* **2022**, *172*, 365–372. [CrossRef]
53. Leist, T.P.; Weissert, R. Cladribine: Mode of action and implications for treatment of multiple sclerosis. *Clin. Neuropharmacol.* **2011**, *34*, 28–35. [CrossRef] [PubMed]

54. Moser, T.; Schwenker, K.; Seiberl, M.; Feige, J.; Akgün, K.; Haschke-Becher, E.; Ziemssen, T.; Sellner, J. Long-term peripheral immune cell profiling reveals further targets of oral cladribine in MS. *Ann. Clin. Transl. Neurol.* **2020**, *7*, 2199–2212. [CrossRef] [PubMed]
55. Moser, T.; Hoepner, L.; Schwenker, K.; Seiberl, M.; Feige, J.; Akgün, K.; Haschke-Becher, E.; Ziemssen, T.; Sellner, J. Cladribine Alters Immune Cell Surface Molecules for Adhesion and Costimulation: Further Insights to the Mode of Action in Multiple Sclerosis. *Cells* **2021**, *10*, 3116. [CrossRef]
56. Sjöström, E.O.; Culot, M.; Leickt, L.; Åstrand, M.; Nordling, E.; Gosselet, F.; Kaiser, C. Transport study of interleukin-1 inhibitors using a human in vitro model of the blood-brain barrier. *Brain Behav. Immun. Health* **2021**, *16*, 100307. [CrossRef] [PubMed]
57. Parker, H.; Ellison, S.M.; Holley, R.J.; O'Leary, C.; Liao, A.; Asadi, J.; Glover, E.; Ghosh, A.; Jones, S.; Wilkinson, F.L.; et al. Haematopoietic stem cell gene therapy with IL-1Ra rescues cognitive loss in mucopolysaccharidosis IIIA. *EMBO Mol. Med.* **2020**, *12*, e11185. [CrossRef]
58. Olcum, M.; Tastan, B.; Kiser, C.; Genc, S.; Genc, K. Microglial NLRP3 inflammasome activation in multiple sclerosis. *Adv. Protein Chem. Struct. Biol.* **2020**, *119*, 247–308. [CrossRef]
59. Polgreen, L.E.; Vehe, R.K.; Rudser, K.; Kunin-Batson, A.; Utz, J.J.; Dickson, P.; Shapiro, E.; Whitley, C.B. Elevated TNF-α is associated with pain and physical disability in mucopolysaccharidosis types I, II, and VI. *Mol. Genet. Metab.* **2016**, *117*, 427–430. [CrossRef]
60. Eliyahu, E.; Wolfson, T.; Ge, Y.; Jepsen, K.J.; Schuchman, E.H.; Simonaro, C.M. Anti-TNF-alpha therapy enhances the effects of enzyme replacement therapy in rats with mucopolysaccharidosis type VI. *PLoS ONE* **2011**, *6*, e22447. [CrossRef]
61. Simonaro, C.M.; Ge, Y.; Eliyahu, E.; He, X.; Jepsen, K.J.; Schuchman, E.H. Involvement of the Toll-like receptor 4 pathway and use of TNF-alpha antagonists for treatment of the mucopolysaccharidoses. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 222–227. [CrossRef]
62. de Oliveira, P.G.; Baldo, G.; Mayer, F.Q.; Martinelli, B.; Meurer, L.; Giugliani, R.; Matte, U.; Xavier, R.M. Characterization of joint disease in mucopolysaccharidosis type I mice. *Int. J. Exp. Pathol.* **2013**, *94*, 305–311. [CrossRef]
63. PhRMA. The PhRMA BRAT Framework for Benefit-Risk Assessment. In *User's Guide to the Process*; PhRMA: Washington, DC, USA, 2011.
64. Schrier, L.; Hadjipanayis, A.; Stiris, T.; Ross-Russell, R.I.; Valiulis, A.; Turner, M.A.; Zhao, W.; De Cock, P.; de Wildt, S.N.; Allegaert, K.; et al. Off-label use of medicines in neonates, infants, children, and adolescents: A joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. *Eur. J. Pediatr.* **2020**, *179*, 839–847. [CrossRef]
65. Castaneda, C.; Nalley, K.; Mannion, C.; Bhattacharyya, P.; Blake, P.; Pecora, A.; Goy, A.; Suh, K.S. Clinical decision support systems for improving diagnostic accuracy and achieving precision medicine. *J. Clin. Bioinform.* **2015**, *5*, 4. [CrossRef] [PubMed]
66. Juhaeri, J. Benefit-risk evaluation: The past, present and future. *Ther. Adv. Drug Saf.* **2019**, *10*, 2042098619871180. [CrossRef] [PubMed]
67. Golde, T.E. The therapeutic importance of understanding mechanisms of neuronal cell death in neurodegenerative disease. *Mol. Neurodegener.* **2009**, *4*, 8. [CrossRef] [PubMed]
68. Li, Y.Y.; Jones, S.J. Drug repositioning for personalized medicine. *Genome Med.* **2012**, *4*, 27. [CrossRef]
69. Bobe, J.R.; De Freitas, J.K.; Glicksberg, B.S. Exploring the Potential for Collaborative Use of an App-Based Platform for n-of-1 Trials Among Healthcare Professionals That Treat Patients with Insomnia. *Front. Psychiatry* **2020**, *11*, 530995. [CrossRef]
70. Mt-Isa, S.; Hallgreen, C.E.; Wang, N.; Callréus, T.; Genov, G.; Hirsch, I.; Hobbiger, S.F.; Hockley, K.S.; Luciani, D.; Phillips, L.D.; et al. Balancing benefit and risk of medicines: A systematic review and classification of available methodologies. *Pharmacoepidemiol. Drug Saf.* **2014**, *23*, 667–678. [CrossRef]
71. Vasilev, F.; Sukhomyasova, A.; Otomo, T. Mucopolysaccharidosis-Plus Syndrome. *Int. J. Mol. Sci.* **2020**, *21*, 421. [CrossRef]
72. Kiykim, E.; Barut, K.; Cansever, M.S.; Zeybek, C.A.; Zubarioglu, T.; Aydin, A.; Kasapcopur, O. Screening Mucopolysaccharidosis Type IX in Patients with Juvenile Idiopathic Arthritis. *JIMD Rep.* **2016**, *25*, 21–24.