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PRACTICAL APPLICATION

Intentional Rechallenge: Does the Benefit Outweigh the Risk?

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Abstract Rechallenge is defined as the readministration of a medication suspected of being a possible cause of an adverse reaction and which has been discontinued as result. It may be unintentional when the appearance of a reaction was initially not attributed to the medication. A rechallenge may be intentional when a prescriber decides that the benefit of rechallenge will outweigh its risk. When considering intentional rechallenge, one should take into account the benefit/risk balance of the suspected causative medication, and the benefit/risk balance of the best available alternative treatment or no treatment. Clinical knowledge is essential in benefit/risk assessment but there is currently no suitable tool to guide the decision on rechallenge. This article aims to propose points to consider in the creation of reaction-specific algorithms for risk assessment and management in the case of drug rechallenge.

1 Introduction

Rechallenge is defined as the readministration of a medication suspected of being a possible cause of an adverse reaction, and which has been discontinued as a result [1]. However, even continued dosing (without discontinuation of treatment), can be regarded as a rechallenge [2]. CIOMS, a global think tank on drug safety, considers rechallenge unacceptable for purely scientific aims and acceptable only when it could be beneficial to an individual subject [3]. The US FDA guidance for Industry on Drug-Induced Liver Injury [4] provides examples of hepatic adverse reactions that are more prone to recur with re-exposure, e.g. cases showing indicators of immunological reaction, such as eosinophilia, rash, fever or other symptoms or findings. Many well-considered recommendations in this guidance could extend to intentional rechallenge with reactions other than liver injury. Most notably, the requirement for assessment of gravity of the initial reaction, close observation of the patient on rechallenge and patient informed consent.

The UK's General Medical Council [5] advises the following when a doctor is prescribing off-label: "the prescriber needs to be satisfied that there is not an appropriately licensed alternative, that there is sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy and take responsibility for prescribing the medicine. They should either oversee the patient's care, monitoring and any follow up treatment or arrange for another doctor to do so and make a clear, accurate and legible record of all medicines prescribed and where this might not be normal practice, as with intentional rechallenge, reasons for prescribing the medicine". Intentional rechallenge and off-label use are different concepts, but similar individualized benefit-risk decisions should be taken into account by the prescriber for each patient when guidance is not provided in the prescribing information or consensus guidelines. When considering rechallenge, the first step is usually the assessment of the likelihood that the reaction was

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caused by the suspected drug. A multitude of published algorithms describe the causality assessment of adverse drug reactions (ADRs), but causality is only one of the factors to be considered in case of intentional rechallenge. The WHO Uppsala Monitoring Centre (WHO UMC) [6] and the Naranjo scale [7] are probably most frequently used to quantify the likelihood of causal relationship. Organ-specific algorithms such as the Roussel Uclaf causality assessment method (RUCAM) [8], Maria-Victorino [9] and ALDEN (algorithm of drug causality for epidermal necrolysis) [10, 13] provide further specificity, the first two for hepatotoxicity and the last for toxic epidermal necrolysis. Either a reaction-specific or a general causality assessment scale fitting the clinical context may be applied; however, these may need to be validated for regulatory purposes or research.

Difficulties occur when there is an unusual temporal relationship between the drug administration and occurrence of the reaction, when the reaction is not expected based on a known mechanism of action of the suspect drug, when such reactions are not frequently encountered with the use of the suspect drug, when the background reporting rate of an event is high (i.e. common and non-specific reactions) making it difficult to ascribe the reaction to the drug, when multiple drugs or other treatments are prescribed, in concomitant diseases, or in a range of other confounding situations. Well-known, expected, i.e. labelled, adverse reactions can be considered to be related to high probability. However, even the labelled reactions, e.g. hepatotoxicity and myotoxicity of statins, can be precipitated by other medical conditions or concomitant xenobiotics and unjustly ascribed solely to the suspect drug.

All effective medications invariably cause some form of adverse reaction. These may be well tolerated by a patient who does not regard them as a safety issue. Hence, even when the causal relationship has been established, or is highly suspected, rechallenge may be justified if the benefit continues to outweigh the risk for that patient. Intentional rechallenge may be ethically more straightforward in situations with low to moderate likelihood that the reaction was caused by the suspected medication. However, what about situations with a high likelihood of causal relationship when an alternative treatment has failed or is not available? In a therapeutic area such as oncology this can be a true therapeutic dilemma. A particular form of rechallenge is desensitization, i.e. induction of temporary clinical unresponsiveness to drug antigens which caused severe hypersensitivity reactions [11]. In this case, the desensitization procedure itself is intentional rechallenge.

To date, we are not aware of any algorithm or decision tree to help healthcare professionals make the right ethical and safe decision. Hence we propose points to consider in the creation of algorithms for clinical decision making in the setting of intentional rechallenge.

2 Published Examples of Rechallenge

The complexity of the benefit-risk decision making required can be illustrated in four published examples.

2.1 Example 1: Fexofenadine

Pinto et al. [12] published a case of rechallenge with fexofenadine given for itching in a patient who presented with syncope. Fexofenadine was believed not to cause QT prolongation linked to cardiac conduction disorders reported with its structurally related compound terfenadine. In this patient, causal relationship was demonstrated, with serial challenge/dechallenge all documented with consistent QT interval changes. Applying the rechallenge algorithm, the acceptable level of toxicity is low with available alternative antihistamines. At the same time, the risk of cardiac arrhythmia in the patient with a suggestive history (syncope) and documented ECG changes indisputably outweighs the potential benefit of symptomatic antihistamine treatment. The investigators monitored patients closely with frequent ECGs in what appears to be a diagnostic rather than therapeutic rechallenge. Patient information/consent was not mentioned. Looking back, rechallenge may have been justifiable before the risk was demonstrated, although based on what we now know further rechallenge would not be justifiable.

2.2 Example 2: Clozapine

Neutropenia and agranulocytosis are recognized serious adverse reactions of clozapine, an antipsychotic drug. Despite the risk of potentially fatal neutropenia, rechallenge is sometimes considered if no other antipsychotic can been found to be efficacious for life-threatening treatment-resistant schizophrenia.

Assessment of individual benefit/risk is somewhat similar to the previously discussed example of QT prolongation since the adverse reaction is acute and the benefits probably life-long. However, in stark contrast to fexofenadine-induced QT prolongation, clozapine-induced neutropenia is less predictable, occurring over a longer period, and with an incompletely defined mechanism (which may be direct toxic or immunoallergic) [13]. This needs to be balanced against the long-term disease burden for the patient, extending to the patient's family and caregivers.

Most psychiatrists choose a trial period of alternative antipsychotics before attempting clozapine rechallenge. This helps determine the benefit/risk balance of alternative treatment for an individual patient, a necessary component of the rechallenge decision-making process. Antipsychotics as a class demonstrate numerous adverse reactions, many of which are observed only after a prolonged treatment period obscuring immediate risk assessment [14].

The medical literature is rich with case reports of negative rechallenge, i.e. successful outcomes without reappearance of neutropenia as well as positive rechallenge [15–18]. Dunk et al. [19] present a cohort of 53 patients from the UK Clozaril patient monitoring system. Rechallenge was usually performed only in cases where the neutropenia or leukopenia is thought unlikely to have been related to clozapine, or in cases of 'mild' neutropenia or leukopenia. Of 53 patients who were rechallenged, 20 (38 %) experienced a further blood dyscrasia. In all but 3 of the 20 patients (85 %) the second blood dyscrasia occurred more quickly than the first. Again, in all but 3 (85 %)—who were different patients—the second blood dyscrasia was more severe than the first (nadir neutrophil count lower than during the first blood dyscrasia).

A general justification for rechallenge at a population level cannot be provided, especially as Dunk et al. [19] were not able to identify reliable predictive factors; however, for an individual severely ill patient who has failed other treatments, the long-term benefit/risk may be positive. Rechallenge of patients with previous agranulocytosis on clozapine is not likely to be justified under any circumstance. Rechallenge in patients with neutropenia (not full agranulocytosis) may be justified but patients have to be closely monitored; however, we should emphasize the importance of providing as much information as possible to the patient and their family so they are aware of the risks based on current evidence.

2.3 Example 3: Agalsidase-β

The reinstitution of agalsidase-β in patients with Fabry disease illustrates a situation that even when the probability and risk of a repeat adverse reaction is high, rechallenge may often be attempted because there is no treatment. Fabry disease is a rare glycosphingolipid storage disorder caused by a deficiency of the lysosomal enzyme a-gal A (a-galactosidase A). The progressive glycosphingolipid accumulation leads to renal, cardiac and cerebrovascular manifestations and early death; hence, that is why individual benefit/risk with regard to rechallenge with agalsidase-β might well be positive [20].

Bodensteiner et al. [21] performed a trial of rechallenge with agalsidase-β in patients withdrawn from a previous trial because of serum IgE antibodies or skin reactivity testing. This study can be singled out as an exemplary case of a detailed rechallenge protocol. An Ethics Committee approved the protocol at each site, and informed consent was obtained from each patient before screening. The dosing regimen was specified, starting with 1/25 of the standard recommended initial infusion rate, the conditions for administration were defined with the availability of the principal investigator and an allergist at the time of rechallenge, and the laboratory monitoring schedule was detailed. Treatment was successfully continued despite numerous reactions, some of which were serious. All patients who withdrew from the study continued treatment with marketed medication.

Neutralizing antibodies must also be considered. Their potential presence should be appropriately investigated as they could lead to loss of efficacy, thereby tilting the benefit/risk balance in a negative direction. This study also ensured that the treatment continues to be of benefit to study subjects by monitoring globotriaosylceramide (GL-3), the biomarker of efficacy. Therefore, benefit/risk balance was continuously assured.

2.4 Example 4: Tobramycin

Hepatotoxicity is not a typical adverse reaction of tobramycin, but it has been described by Nisly et al. [22] and is in the summary of product characteristics for tobramycin. The article describes a 20-year-old patient with osteomyelitis with positive dechallenge and normalization of liver function tests within a week of tobramycin discontinuation. Serial dechallenge and negative rechallenge of other antibiotics suggested that tobramycin was implicated. In contrast to other examples in this article, this rechallenge consists of continued dosing rather than interruption followed by reinstitution. Also, rechallenge was unintentional in the sense that tobramycin was not recognized by the individual prescriber as being causally related to the hepatic adverse reaction. It was only when the reaction became more severe with dose increase and resolved upon dechallenge that the prescribing doctors associated tobramycin with hepatotoxicity.

In this example, several medications were prescribed simultaneously so that the likelihood of causal relationship with tobramycin was not initially obvious. Drug benefit was medically significant, as tobramycin was prescribed for the treatment of *Pseudomonas aeruginosa* bacteraemia and osteomyelitis for which there are limited antibiotic options, which individually depends on the antibiotic susceptibility and treatment available locally.

This example also illustrates the dynamics of the assessment and reassessment based on accumulating data. Liver function testing following dose increase and dechallenge gave fresh insight into the likelihood of the suspected causal relationship. Microbiological sensitivity monitoring enables assessment of alternative antibiotics for the continuing reassessment of benefit/risk for an individual patient. Over time, the patient's doctors concluded that the likelihood of causal relationship between liver dysfunction and tobramycin became so strong and so negative for the individual benefit/risk balance that continuing rechallenge became unacceptable.

3 Points to Consider

Justifying rechallenge depends on examining evidence to see whether there is no available alternative that may confer the same benefit. A prescriber should further examine the risk in detail and the potential predictive risk factors for an individual reaction so that risk minimization measures can be implemented, where possible. These risk minimization measures are not only specific to each drug, but even more, they should be specifically tailored to each significant adverse reaction and specifically interpreted for each individual patient [23]. In routine clinical practice this would apply to adverse reactions that most frequently lead to treatment discontinuation. However, how can we pull such disparate evidence together to create a useful algorithm to help individual clinicians justify rechallenge under controlled circumstances? We therefore advise that before attempting rechallenge the treating physician must consider the following (see Fig. 1):

Benefit assessment:

- The real need of the drug: Often the adverse reaction happens with a drug that has valid alternatives. The administration of the alternative drug may be without discomfort and should not have a higher probability to induce ADRs. In the presence of a valid alternative, rechallenge is not ethically justified.
- Benefit assessment for both suspect and alternative treatment should be based on clinical trial efficacy results in the given patient population. The effectiveness for the particular patient might also be known if the patient was treated long enough to assess it. The alternative treatment is assessed in a similar manner as the suspect drug, the key difference being that there may not have been a previous challenge with the alternative treatment and the patient's response to alternative treatment may be unknown. If both suspect and alternative drugs are from the same class or cause similar adverse reactions (for example bleeding events in deciding between two anticoagulants), a comparative estimate of both benefit and risk may be possible. The CIOMS Working Group IV provides good general guidance on benefit and risk assessment [24].
- The acceptable level of risk should be justified by the expected benefit. The final result of a benefit assessment is a defined threshold above which the risk is not justified by the expected benefit. Complete withdrawal of medical treatment may be considered. In such a case, the risk of disease worsening and progression in the absence of treatment should be taken into account instead of the risk of alternative treatment.

Risk assessment:

- Estimate the characteristics of the reaction that may occur upon rechallenge: this is particularly the case for immunological hypersensitivity reactions in which prior sensitization has occurred as the reaction may occur earlier and may be more severe on rechallenge.

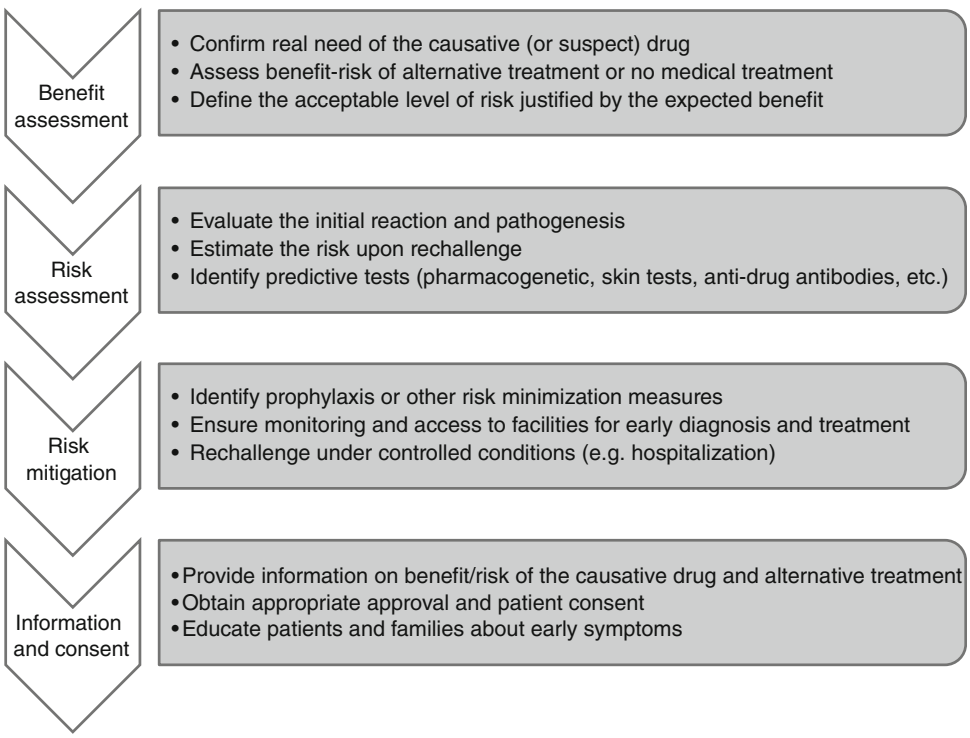

Fig. 1 Points to consider in clinical decision making in the setting of intentional rechallenge

The mechanism of adverse reaction may or may not be known; the severity, time of onset and response to previous treatment of the reaction should be considered.

- Note that the risk of rechallenge is not equivalent to the risk of the initial reaction that caused suspicion that the drug was causative. Instead, the risk of rechallenge is the reasonably expected risk of the reaction if it were to reoccur and that it might be more severe should it occur again. Likelihood that the suspect drug was causative is essential at this point.
- Identify patients with risk factors based on characteristics of the initial reaction and medical history which may predispose to higher risk: Pharmacogenomic studies, in particular, have been able to identify strong genetic predisposing factors for hypersensitivity reactions to carbamazepine, abacavir and allopurinol. With the expanding use of pharmacogenomics, this list will surely continue to expand [25]. When available, use in vitro tests (e.g. β-lactams, cephalosporins) before the new administration of drug [26]. For biological drugs in particular, antidrug antibodies may be useful in predicting the likelihood of reactions [27].

Risk mitigation:

- Identify appropriate prophylaxis based on best available evidence to mitigate or prevent the anticipated reaction, even though this may be limited to 'expert opinion'. The best treatment of the reaction may not be known but should be proactively considered.
- Define the requirements for monitoring a possible adverse reaction, such as the variables to be measured, the interval of testing and examination, and a point in time at which further monitoring may no longer be required. Ensuring follow-up at appropriate intervals is particularly applicable to reactions that take longer time to develop and for which certain laboratory or clinical markers can be used for early identification. Such a monitoring schedule is likely to be more intensive than what is currently in the manufacturers' product information leaflets. Hence, a structured and adapted written plan of action based on the algorithm is recommended. Such a plan would serve a dual purpose—as a basis for explaining an individual physician's action to a local ethics committee, and as a practical guide for the clinician and their team, which can be recorded in the patient's notes.
- Performing rechallenge under controlled conditions (e.g. inpatient hospitalization during rechallenge, intensive care unit) minimizes the risk if the precautions are taken to prevent or promptly treat the recurring reaction. Qualified and informed personnel, and appropriate diagnostic as well as therapeutic measures that may be potentially required, should be readily available. This particularly applies to immediate reactions, e.g. immediate hypersensitivity reactions. This approach must be rational, depending on the expected time of insurgence of the reaction; late reactions need prolonged observations. Reinitiating administration at a lower dose and gradually increasing it may help minimize the risk. Usually, administration should reach the therapeutic dosage to exclude a possible reaction at higher doses.

Information and consent:

- We emphasize the importance of patients (and their families in the case of patient mental incapacity) to provide informed consent to rechallenge (once the rationale of the need for rechallenge is defined). The consent should provide information on the benefit/risk balance of the available treatment alternatives.
- The informed consent and the rechallenge algorithm may require approval from an appropriate clinical ethics committee or other comparable body monitoring prescribing decisions. This depends on the specific case and local requirements, as well as the settings, e.g. routine clinical use or clinical trials. In any case, rechallenge cannot be performed without due ethical consideration for patient autonomy so that acts of rechallenge must be intentional, voluntary and based on full understanding of the circumstances.
- Authorized patient information leaflets should already contain general information on expected adverse reactions. However, this information may need to be supplemented by additional information customized for a particular therapeutic situation. There should be sufficient emphasis and specific advice about the likelihood of reaction recurrence and what to do should it occur. Patients and their families should be educated about early symptoms of possible adverse reactions and action required, e.g. to promptly seek medical advice for certain prodromes of expected adverse reactions.

4 Discussion and Recommendations

The need to consider rechallenge after a suspected reaction applies through clinical drug development to marketing. Sponsors could create rechallenge algorithms in the pre-authorization phases as part of a developmental risk management plan. In early phases of development, both risks and benefits may be poorly characterized, further complicating rechallenge considerations. Because of liability concerns, licence holders would be understandably reluctant to create rechallenge algorithms, unless they were part of an approved risk management plan.

Prescribing physicians should not act in isolation. They should carefully document their actions systematically in

risky situations, such as intentional rechallenge. The proposed algorithm is meant to aid the thought process and stimulate further debate as further guidance on specific situations may well be required. At the present time, intentional and recurrent rechallenge in a patient series is often performed by specialist centres that have available personnel for monitoring and intensive care, e.g. allergy centres performing desensitization. For marketed drugs, expert societies or specialist centres would be most competent to further develop algorithms to support prescribing professionals. In their absence, patients may continue to be exposed to random benefit/risk assessment by physicians who may not be fully informed of evidence-based recommendations. Whatever the context may be, the best practice for rechallenge should be considered and guidance provided to individual prescribers.

These algorithms might initially be conservative and restrictive. However, as safety evidence from unintentional and intentional rechallenge accumulates based on the use of such algorithms, then the threshold for rechallenge may be lowered and the algorithm appropriately modified. Both positive and negative rechallenge situations add valuable information and companies should seek additional data from medical queries in all cases in order to generate a body of evidence about real-life use of a medicine.

In light of renewed emphasis on deterring of medication errors and off-label use in European pharmacovigilance legislation, applying these regulations must not inadvertently interfere with responsible prescribing of essential medicines. The worry is that such use may, in a regulatory sense, be viewed as medication error, misuse or off-label use. Hence, intentional rechallenge as a result of thoughtful deliberation of benefit/risk should be differentiated from accidental rechallenge and a medication error, even if the rechallenge ultimately proves to be harmful.

5 Conclusion

Each significant adverse reaction potentially leading to treatment discontinuation should have a reaction-specific rechallenge algorithm. Evidence-based risk assessment and minimization measures should be proposed as a collaborative effort by drug manufacturers, expert centres or professional societies. All such focussed activities should be addressed as part of active risk management planning. However, ultimately the ethical and safety responsibility rests with the individual prescribers and patients.

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