"Maybe it’s not"
or
Primum non nocere et optimum curare

Vid Stanulovic, MD, PhD
Is it always too dangerous?

Rechallenge can be dangerous;

The risk may be minimized in certain situations. Or there may be no risk at all;

Whatever the risk may be - how should we manage it?

How to gather evidence and provide guidance on justifiable rechallenge scenarios?
Why not rechallenge?

**Medicolegal/commercial basis:**
- Financial/strategic risk for sponsors. Fear of halting development and insurance claims;
- Medicolegal burden for investigators and prescribers. Fear of malpractice claims.

**Scientific basis:**
- We assume that some unknown susceptibility to the ADR (an idiosyncrasy) exists in this patient and other small (?) number of patients;
- Evidence or a reasonable hypothesis, to believe that the ADR will occur in this patient, but not in the vast majority of others which we keep on treating;
Why consider rechallenge?

- If a patient is enrolled, it is believed that the expected benefits initially outweigh the potential risks;

- Consider particularly rare/neglected diseases with limited treatment options;

- Reconsider rechallenge in case of failure or intolerance to second line therapies;

- Only if we have adequate prior knowledge-base to expect that B/R may be favorable in the given patient. Rechallenge is a « N=1 clinical trial [1];

Alternative to rechallenge – premature discontinuation

Threshold for prematurely discontinuing patients is generally low following suspected ADRs;
- Result: high discontinuation rate due to suspected ADRs;

Assumption: guilty until proven innocent;
- High likelihood of causal relationship;
- Possible idiosyncrasy, fulminant, unpredictable onset and evolution even in case of mild or moderate initial reaction;
- Reaction is not closely dose-related, hence low dose would lead to an equally or more dramatic or irreversible reaction;
- Risk-minimization (prophylaxis, monitoring and early identification of recurring reaction, treatment etc) not established or not possible;

Alternative approach to evaluation of suspected ADRs:
- Retrospective evaluation of prematurely withdrawn patients;
General rechallenge algorithm

**Benefit assessment**
- Confirm real need of the causative (or suspect) drug
- Assess benefit-risk of alternative treatment or no medical treatment
- Define the acceptable level of risk justified by the expected benefit

**Risk assessment**
- Evaluate the initial reaction and pathogenesis
- Estimate the risk upon rechallenge
- Identify predictive tests (pharmacogenetic, skin tests, anti-drug antibodies, etc)

**Risk mitigation**
- Identify prophylaxis or other risk minimization measures
- Ensure monitoring and access to facilities for early diagnosis and treatment
- Rechallenge under controlled conditions (e.g. hospitalisation)

**Information and consent**
- Provide information on benefit/risk of the causative drug and alternative treatment
- Obtain appropriate approval and patient consent
- Educate patients and families about early symptoms

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Specific, focused algorithms

Each ADR is unique and each drug-ADR combination requires a unique approach in evaluating benefit/risk, risk minimization and ethics of rechallenge;

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PRACTICAL APPLICATION

Intentional Rechallenge: Does the Benefit Outweigh the Risk?

Vid Stanulović · Mauro Venegoni · Brian Edwards
Benefit

- Often the adverse reaction happens with a drug that has valid alternatives;
- Anticipated benefit may be marginal compared to possible risk;
- The administration of the alternative drug may be without discomfort and should not have a higher probability to induce ADR;
- In all of the above, there is no room for rechallenge;
- Benefit of second-line therapy comparable?
- Failure of second-line therapy may prompt reconsideration of the initially dechallenged;
  - third-line i.e. fall-back to first line;

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Risk

Suspected mechanism crucial in decision making;

Biomarkers, predictors, pharmacogenetics, antibodies (e.g. autoimmunity hepatitis) and other tests...

Likelihood of causal relationship, confounders, drug-drug/disease/food interactions...

High number of abnormal LFT findings in general healthy population;

Risk of rechallenge ≠ risk of the initial reaction:
- May be higher due to sensitization or already induced damage;
- May be lower if risk minimization is effective;
- May be no risk at all;

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Risk mitigation

- **Prophylaxis to mitigate or prevent the ADR.** However, hepatoprotectors, such as acetylcysteine, unfortunately limited in DILI;

- **Timing of LFT and other monitoring to detect early;**

- **Treatment of the reaction may not be known but should be considered and made available;**

- **Performing rechallenge under controlled conditions (e.g. inpatient hospitalization);**

- **Reinitiating administration at a lower dose and gradually increasing it may help minimize the risk – equivalent to phase I dose-escalation;**
Rechallenge consent

- Authorized patient information should already contain general information on expected reactions;

- The specific **rechallenge consent** focuses on the particular, expected, already experienced reaction;

- An addendum to a clinical trial consent, or a specifically developed consent if unanticipated reaction;

- Highlight benefit/risk of available alternative treatments;

- Specific advice about the likelihood of reaction recurrence and what to do should it occur;

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Examples of acceptable and successful rechallenge

Drug desensitization is a commonly used and universally accepted therapeutic rechallenge [1]; Rechallenge protocols have been successful despite high likelihood of life-threatening ADRs [2];

2. Bodensteiner D et al. Successful reinstitution of agalsidase beta therapy in Fabry disease patients with previous IgE-antibody or skin-test reactivity to the
Examples of DILI rechallenge

A comprehensive search of GSK adverse events (1958–2007) identified 648 “possible drug-related hepatic disorders”, of which medically confirmed cases included:

- 648 positive rechallenge with 88 cases of possible or probable DILI, including 2 fatal, and
- 441 negative rechallenge [1];

Rechallenge not attempted xxx,xxx ?

The true incidence of negative rechallenge is probably much higher as such negative cases are unlikely to be reported. This highlights the number of patients who are unjustly deprived of their first-line treatment because of a suspicion of an adverse drug reaction [2];

THE NATIONAL HALOTHANE STUDY

A STUDY OF THE POSSIBLE ASSOCIATION BETWEEN
HALOTHANE ANESTHESIA AND POSTOPERATIVE
HEPATIC NECROSIS

Report of
The Subcommittee on the National Halothane Study,
of the Committee on Anesthesia, Division of Medical Sciences,
National Academy of Sciences-National Research Council
Washington, D.C.

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With the issue unresolved, and perhaps unresolvable, how should one proceed clinically? It is clearly unwarranted to suggest that halothane anesthesia should not be repeated, for it is under the difficult circumstances of emergency reoperation that a wide choice of anesthetic agents may be most urgently needed. Furthermore, it would not be justifiable to suggest that halothane should not be used for more than one purely elective operation. When, however, a patient has suffered unexplained fever and jaundice after administration of halothane, it is the opinion of some physicians that halothane should not be used for a subsequent operation. The basis for their recommendation is the usual medical doctrine that any treatment followed by ill effects should ordinarily not be repeated. Whatever the merits of such a recommendation, it is remarkable that there was not a single patient in the National Halothane Study who was jaundiced after the administration of halothane and died after a second administration and was found at necropsy to have suffered massive or intermediate hepatic necrosis.

Halothane: Rechallenge or reexposure?

Of 14 patients who had repeat surgery, 4 died. In 10 patients massive liver necrosis developed less than three weeks after halothane anesthesia, and 27 (77 per cent) of these had multiple exposures to halothane [1].

Post-Halothane Jaundice in Relation to Previous Administration of Halothane

WILLIAM W. MUSHERN, M. ROSEN, E. V. JONES

British Medical Journal, 1971, 1, 333–333

Summary

The time interval since previous anaesthesia was compared in a surgical population in South Wales and in patients who developed jaundice after halothane. There was a significant difference in the pattern of time interval since previous general anaesthetics in the surgical population and in those patients who developed jaundice after halothane. In the group who developed jaundice there was an “excess” of patients who had had a previous halothane anaesthetic within four weeks. Halothane should if possible be avoided in patients who have had it before, particularly if this was within the previous four weeks. In the case of repeat halothane anaesthetics within four weeks, the risk seems to lie between 1 in 6,000 and 1 in 22,000.


The true dangerous, often idiosyncratic, ADRs should be isolated and rechallenge contraindicated;

Blanket contraindication to rechallenge may result in more harm than the potentially harmful rechallenge;

Unless cautious rechallenge is evaluated in clinical trials based on available evidence, it may be attempted in the « real-world » under suboptimal conditions;

Medicolegal aspects should not take precedence over scientifically founded algorithms approved by EC/IRBs and other relevant bodies;

A framework and guidance is required for rechallenge within clinical trials and RMPs ideally evaluated pre-authorization;
Way forward (conclusions 2)

We cannot continue turning the blind eye and leaving the burden and responsibility on individual treating physicians to evaluate the risk/benefit;

Prescribing information, ideally, should contain the available clinical evidence, highlighting unacceptable rechallenge and guiding justifiable scenarios;

No scientific interest can ever take precedence over the benefit justifying the risk in the individual who requires treatment and provides fully informed and uninfluenced consent.
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Back-up slides
Just an example - statin hepatotoxicity

A 52-year-old man developed DILI 12h after fluvastatin 80 mg/d for unstable angina. He developed increasing nausea, upper abdominal pain and anorexia. Examination revealed a body temperature of 38.5 C and abdominal tenderness. Tests revealed an elevated WBC count, AST 578 U/L, ALT 421 U/L, GGT 522 U/L, ALP 115 U/L and total bilirubin 54.4 mmol/L. Fluvastatin was withdrawn. Within 1 week, anorexia, fatigue and abdominal pain had improved, liver biochemistries were almost normal.

Approximately 1 year later, the man received fluvastatin 80 mg/day again. He presented with similar symptoms, and liver enzymes increased to their peak within 48h. Fluvastatin was discontinued, and within 1 week anorexia, abdominal pain and fatigue improved. Within 3 weeks, his liver biochemistries normalized.

Li et al. Am J of Therapeutics, 23: e318-20, No. 1, Jan-Feb 2016
Statin hepatotoxicity

- Generally mild, dose-dependent and reversible.
- DILI Network: Presentation highly variable:
  - All commonly used statins implicated;
  - Nine patients with cholestatic hepatitis, 12 patients hepatocellular injury of which 6 had an autoimmune phenotype. Four patients chronic liver injury of which 3 had an autoimmune phenotype. [1]
- One could estimate that 1–10% of those taking statins have been denied the benefit of statins as a result of unwarranted concern; [2, 3]
- So, can we rechallenge statins after DILI?

Realistic view

Because of liability concerns, it is unlikely that sponsors would prepare intentional rechallenge algorithms unless mandated, described in clinical trial protocols or an approved RMP;

It is unlikely that the main clinical trial protocols will contain rechallenge algorithms unless it is dose modification for clearly dose-related reactions. However, specific protocols or substudies may be developed.

Following marketing approval, expert societies or medical associations may be more likely to provide recommendations to support prescribing professionals, based on individual experiences;

Unless rechallenge is described in the PI, rechallenge may be regarded as off-label use;