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CURRENT CLINICAL CONTROVERSY

# An 'Adaptive Treatment Strategy' for Oral Vancomycin in Patients with the Orphan Disease Primary Sclerosing Cholangitis

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## Abstract

Decision-making in clinical medicine ideally is based upon evidence from randomized, placebo-controlled trials (RCTs) and subsequent systematic reviews and meta-analyses. However, for orphan diseases, the expectation of having one or multiple RCTs that inform clinical guidelines or justify specific treatments can be unrealistic and subsequent therapeutic nihilism can be detrimental to patients. This article discusses the benefits of therapeutic decision-making in the context of orphan diseases, focusing on primary sclerosing cholangitis (PSC) as an example of an orphan disease with poor clinical outcomes. PSC is a rare disorder characterized by inflammation and progressive fibrosis of the bile ducts. It carries a high risk of liver failure, malignancies, and debilitating symptoms that impair quality of life. Liver transplantation is currently the only life-prolonging intervention for PSC, but it is not a curative option. The article highlights the potential benefits of treating PSC patients with oral vancomycin (OV), which has shown significant clinical responses and improved quality of life in some cases. However, access to OV therapy is limited due to the lack of RCTs supporting its use. The standard requirement of having evidence from RCTs may result in withholding potentially life-altering and/or life-saving treatments for patients with orphan diseases. Conducting RCTs is challenging in these patient populations due to difficulties in recruiting the required patient cohorts and limited commercial returns. A standardized 'adaptive treatment strategy' is proposed to address this. This approach leverages the best available evidence for specific treatments, considers individual clinical responses, and adjusts treatment over time.

**Keywords** Orphan disease · Rare disease · Therapeutic decision-making · Adaptive treatment strategy · Primary sclerosing cholangitis · Oral vancomycin

Therapeutic decision-making in medicine requires careful consideration of the available evidence in relation to benefits, potential harm, and costs for specific treatments or even no treatment [1]. This decision-making is ideally guided by clinical practice guidelines informed by randomized, placebo-controlled trials (RCTs) or systematic reviews and meta-analysis that summarize the available evidence. Patient involvement is increasingly recognized as important for the development of clinical guidelines, and concerns have been raised regarding guidelines developed without this input. Ultimately, the guideline development process is intended to maximize benefits and ensure that clinical decision-making is not inappropriately distorted by biases of healthcare payors, policymakers, funding agencies, or providers. However, for orphan diseases—particularly if repurposed medications are considered—the requirement of evidence from RCTs to develop guidelines or justify specific treatments/interventions can be problematic even if the regulatory requirements are lowered [2]. Therapeutic nihilism due to the absence of the usual supportive (i.e., RCT) data

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for off-patent repurposed drugs may be neither in the best interest of patients nor society.

While the regulatory frameworks for the drug development for orphan diseases are favorable (shorter development and approval timelines, additional financial research and development incentives, higher clinical trial and FDA success rates, stricter and extended market exclusivity, lower marketing costs, faster uptake, and high reimbursed prices) [2], on the other hand, the low disease prevalence and complex natural history combined with a low return of investment for repurposed off-label medications may limit the ability of pharmaceutical companies to generate profits with such drugs. Interestingly, regarding the value of pharmaceutical companies, no significant difference was observed between companies developing orphan and non-orphan designated lead products [2]. Indeed, one recent study concluded that economic conditions surrounding orphan-designated drugs translate to a favorable financial risk-return profile for bioentrepreneurs and investors [3]. Nevertheless, the repurposing of existing off-patent drugs might be hampered by the absence of commercially leverageable intellectual property. Thus, the generation of evidence from RCTs for repurposed off-patent drugs may be unrealistic for orphan diseases and other diseases, and as such potentially effective therapies may be withheld. While it is acknowledged that the barriers to get regulatory approval for novel treatments are lowered for orphan diseases [4], this does not address the challenges with off-patent medications. Even though there are other innovative trial designs (e.g., basket or umbrella trials) that are suitable for orphan diseases, they are resource intensive due to operational complexity and the need to manage multiple parallel sub-studies [5].

Here, we discuss how therapeutic decision-making might be utilized in a setting where data from RCTs are unavailable for patients with orphan diseases, especially ones with high morbidity and mortality, such as primary sclerosing cholangitis (PSC). In such cases, there may be an off-patent treatment option that has not undergone proper registration but could still potentially offer significant clinical benefits to these patients.

PSC is a rare disease with the highest prevalence in North America and western Europe, where incidence and prevalence are approximately 1–1.5 cases per 100,000 person-years and 6–16 cases per 100,000, respectively [6]. PSC is characterized by inflammation and progressive fibrosis of the bile ducts ultimately leading to end stage liver disease (ESLD). PSC also carries an increased risk of malignancies affecting the liver, bile ducts, or colon, and these malignancies may manifest before progression to ESLD. Nearly 75% of PSC patients have associated inflammatory bowel disease, IBD [6], which has lent credence to the PSC–microbiome hypothesis [7] and the identification of a unique intestinal microbial profile in PSC [8, 9]. In part because of this, PSC-IBD is believed to represent a unique form of IBD [10], distinct from ulcerative colitis or Crohn's disease. Regarding pathophysiology, PSC is generally considered a complex, immune-mediated disorder [6]. Nevertheless, treatment with immunosuppressive agents has shown to have minimal clinical benefit in PSC, and thus far there is no *accepted* therapy to halt PSC disease progression [6]. Thus, liver transplantation (LT) is the only life-prolonging intervention for patients with PSC and ESLD [6]. Indeed, in many countries including the US [11, 12], PSC is now among the leading indications for LT. PSC frequently recurs post-LT in 10–37% of transplant recipients [13], with the highest rates seen in pediatric and living donor-LT patients [14]. Without LT, median life expectancy is 17–21 years in adults and 12 years in children [15, 16]. Morbidity of patients with PSC is characterized not only by the progressive liver failure, but a very high risk to develop cholangiocarcinoma as well as hepatobiliary, pancreatic, gallbladder, and colorectal cancers [17]. During the disease course, patients with PSC frequently experience debilitating symptoms that impair quality of life (QoL), including severe fatigue, pain, gut-related symptoms, and/or pruritus [18–20]. The therapeutic dilemma (challenge) that PSC patients, their families, and ultimately society face is a severely reduced life-expectancy and a debilitating QoL, with only LT as an accepted life-extending but not necessarily curative therapeutic option because of the common recurrence of the disease in the allograft.

In 1998, Cox and Cox [21], reported beneficial effects of treating three paediatric PSC patients with oral vancomycin (OV). Subsequently, multiple published clinical trials, case series, and other reports, have shown that OV treatment for PSC patients can result in significant clinical responses [10], allowing patients to avoid colectomies, LTs, and hospitalizations and to have a relatively normal QoL [22]. These benefits are seen in a large proportion of OV-treated PSC patients, especially when treatment is initiated at a relatively early stage of liver disease. There is also considerable benefit in relation to the associated IBD, with clinical and endoscopic remission achieved in most patients even if they have failed conventional IBD therapies. Data underscore not only the potential benefit of OV in patients with PSC, but also its safety and low risk of adverse events (AEs), even if used over an extended period, including a negligible risk of developing vancomycin resistant enterococci, VRE [23]. Though not all patients with PSC have a positive response to OV therapy (reportedly used in varying doses, ranging from 250 to 3000 mg daily as a maintenance therapy) [16] a subset of patients experience dramatic improvements in intestinal and hepatobiliary manifestations. The precise mechanisms of action of OV in PSC are yet unknown. However, OV has been found to be acting as both an antimicrobial agent and an immunomodulator. Potential mechanisms of action

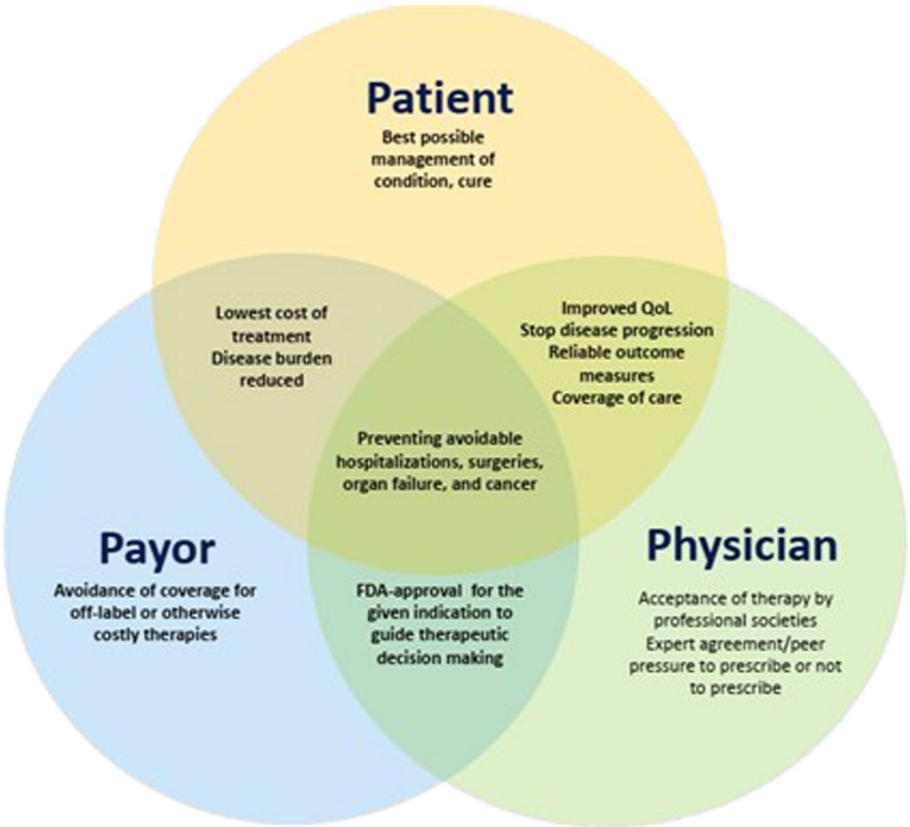


**Fig. 1** Schematic representation of the intersection of patient, physician, and payor interests

include selective targeting of Gram-positive species due to its narrow antibiotic spectrum, reduction of hydrophobic secondary bile acids linked to right-sided colitis and bile duct injury, and immunomodulatory effects of vancomycin on inflammatory pathways like tumour necrosis factor (TNF)-alpha and/or downregulation of Treg induction [23].

Nonetheless, access to OV therapy for PSC is limited primarily because of the lack of approval for this indication due to the lack of RCTs. Therefore, most PSC patients are denied funding or reimbursement for this potentially life-altering and/or lifesaving therapy. More than 20 years after the first clinical observation that this therapy improves PSC [21], there are now three RCTs that are in progress to study OV therapy for patients with PSC (EudraCT 2022-000875-37; NCT03710122; ACTRN12621000792820) the results of which will supplement the demonstrated effectiveness of OV for PSC in the two previous small RCTs [24, 25]. Yet, the results of these current three RCTs are years away and it is important for patients with PSC to have a current option to trial OV. These ongoing RCTS will hopefully prioritize examining the impact of therapeutic options on the natural progression of PSC and clinically significant outcomes, such as the necessity for liver transplantation, progression to cirrhosis, or the incidence of cancer. Indeed, a recent large multicentre paediatric cohort study revealed that OV was associated with greater odds of clinical of the gut-related symptoms in patients with PSC-IBD [26].

Given the challenges to achieve registration for a repurposed, off-patent medication to treat an orphan disease, patients, payors, and society would benefit from the creation of special pathways to facilitate access. Experts should be able to utilize therapies with supportive data other than RCTs with the ultimate objective of providing safe, effective, and cost-efficient therapies. In addition to published data, this could include real-world data such as electronic health records, insurance claims databases, patient registries, and other healthcare data sources. Over time, by establishing comprehensive patient registries and coordinating data sources that integrate clinical, genetic, and biologic information, healthcare professionals can better collaborate and share knowledge regarding orphan diseases and patient responses to repurposed, off-patent medications. Furthermore, this will facilitate quicker and more effective dissemination of information to improve patient care, as well as support the development of strong evidence through multicenter research studies. Incentives such as tax breaks, market exclusivity, exemptions from user fees, and other measures can be implemented to specifically encourage the development of treatments for rare diseases.

Patients with orphan diseases that have without treatment a high risk of substantial morbidity and mortality should

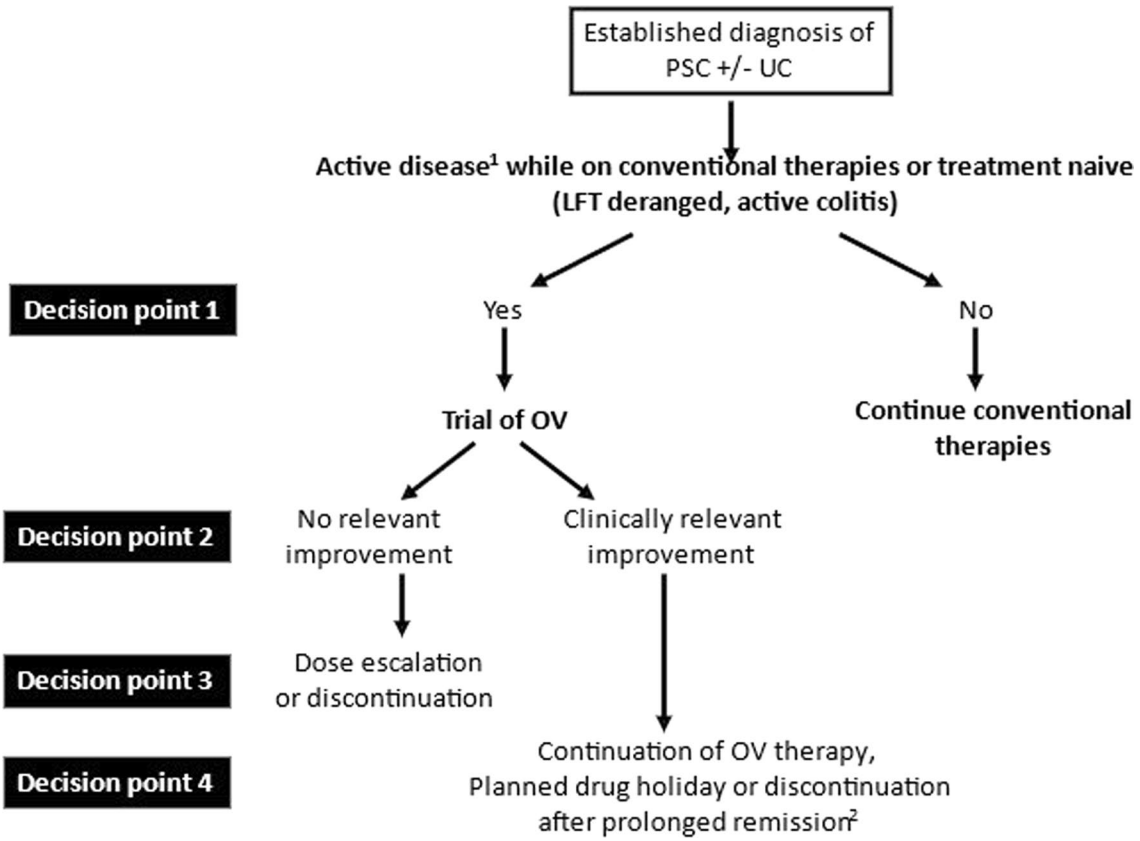


**Fig. 2** Proposed adaptive treatment strategy to trial oral vancomycin (OV) therapy in patients with primary sclerosing cholangitis (PSC) with or without ulcerative colitis [+/− (UC)]. This algorithm may be applicable for other similar orphan diseases. [1]May include persistently abnormal and/or worsening serum liver tests, cholangiographic findings, and/or symptoms, active IBD, and other features. [2]A therapeutic drug holiday may be considered to assess for recrudescence of active disease or to permit trial of novel therapies that enter the market

be provided access to treatments that have demonstrated in cohort studies (or other forms of non-RCT clinical evidence) to be reasonably safe, effective, and without excessive economic burden to payors. The risk–benefit analysis should be in favour of such treatment(s).

While therapeutic decision making may appear simple when informed by the appropriate evidence from clinical trials, there are many stakeholders with interests that are only partly aligned with the expectations and perceived needs of patients (Fig. 1). Patients deem QoL, the avoidance of hospitalizations, major surgeries including organ transplant, cancer development, and/or death as more important outcomes than blood markers or risk scores. They rarely make therapeutic decisions solely on the basis of whether experts agree that a therapy is proven by a RCT. Ideally, therapeutic decision-making would provide orphan disease patients a chance to benefit from interventions that are supported only by lower-level evidence (as compared to RCTs), payors the possibility of avoiding costly adverse events, and clinicians an opportunity to improve health outcomes as well as a window through which they may gain experience with this therapy. This framework may be applied to numerous orphan diseases and otherwise understudied disorders.

Based on the above, we propose an 'adaptive treatment strategy' for PSC, which can be applied for other similar orphan diseases and otherwise understudied disorders, but likely only for repurposed drugs. Utilizing 'best-available evidence' and established cost–benefit analyses, treatment is initiated, and the course of treatment is adjusted over time depending on the patient's response. A patient not responding to the initial dose of a given treatment may consider drug dose and/or bioavailability adjustment, and eventual discontinuation if no response. Patients who respond and/or achieve remission may opt to discontinue the treatment and re-initiate treatment upon return of disease symptoms to ensure that treatment truly was associated with improvement of objective and subjective disease markers. This ensures that patients with spontaneous remission are not overtreated (Fig. 2). Given data regarding PSC treatment are limited, following this or a similar uniform approach

internationally can facilitate organization, review, and publication of treatment-related data, augment the knowledge base, and further inform therapeutic decision-making. These data would guide the 'adaptive treatment strategy'. However, while this approach does not replace proper RCTs, it but could bridge the time until the required data are available. Properly designed RCTs remain the 'gold' standard and even if an 'adaptive treatment strategy' is used, the ultimate goal is to have treatments with efficacy proven in RCTs. It also needs to be emphasized that the 'adaptive treatment strategy' is only suitable for repurposed (registered) treatments with well-established safety profiles.

Patients affected by orphan diseases are disadvantaged by the current approval processes for therapies that heavily rely on RCT data. Despite regulatory adjustments that facilitate the approval of novel treatments for orphan diseases, significant barriers remain. This is particularly true when off-patent treatments are repurposed and will not provide the required return of investment if traditional RCTs are required. Adaptive therapeutic decision-making in orphan diseases will lead to a 'snowball effect:' more patients in trials means more data, stronger evidence, and increased confidence in drug use. A 'holistic approval process' of supporting 'adaptive treatment strategies' would address the unmet needs of patients affected by orphan diseases by considering the potential benefits and risks of a given therapy while also considering the total cost to society for no therapy.

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## Declarations

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