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MINIREVIEWS

Pitfalls and promises of bile duct alternatives: A narrative review

Mitsuo Miyazawa, Masayasu Aikawa, Junpei Takashima, Hirotoshi Kobayashi, Shunsuke Ohnishi, Yoshito Ikada

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Mitsuo Miyazawa, Junpei Takashima, Hirotoshi Kobayashi, Department of Surgery, Teikyo University Mizonokuch Hospital, Kanagawa 213-8507, Japan

Masayasu Aikawa, Department of Surgery, Saitama Medical University International Medical Center, Saitama 350-1298, Japan

Shunsuke Ohnishi, Department of Gastroenterology and Hepatology, Hokkaido University Faculty of Medicine and Graduate School of Medicine, Sapporo 060-8638, Japan

Yoshito Ikada, Department of Bioenvironmental Medicine, Nara Medical University, Nara 634-8521, Japan

Corresponding author: Mitsuo Miyazawa, FACS, MD, PhD, Professor, Department of Surgery, Teikyo University Mizonokuch Hospital, 5-1-1 Futago, Takatsu-ku, Kawasaki-shi, Kanagawa 213-8507, Japan. mmiyazawa@med.teikyo-u.ac.jp

Abstract

Biliodigestive anastomosis between the extrahepatic bile duct and the intestine for bile duct disease is a gastrointestinal reconstruction that abolishes duodenal papilla function and frequently causes retrograde cholangitis. This chronic inflammation can cause liver dysfunction, liver abscess, and even bile duct cancer. Although research has been conducted for over 100 years to directly repair bile duct defects with alternatives, no bile duct substitute (BDS) has been developed. This narrative review confirms our understanding of why bile duct alternatives have not been developed and explains the clinical applicability of BDSs in the near future. We searched the PubMed electronic database to identify studies conducted to develop BDSs until December 2021 and identified studies in English. Two independent reviewers reviewed studies on large animals with 8 or more cases. Four types of BDSs prevail: Autologous tissue, non-bioabsorbable material, bioabsorbable material, and others (decellularized tissue, 3D-printed structures, *etc.*). In most studies, BDSs failed due to obstruction of the lumen or stenosis of the anastomosis with the native bile duct. BDS has not been developed primarily because control of bile duct wound healing and regeneration has not been elucidated. A BDS expected to be clinically applied in the near future incorporates a bioabsorbable material that allows for regeneration of the bile duct outside the BDS.

Key Words: Bile duct alternative; Bile duct substitute; Biliary regeneration; Bile duct reconstruction; Peribiliary gland; Bioabsorbable polymer

Core Tip: The bile duct-intestinal anastomosis eliminating the function of the papilla of Vater causes chronic inflammation due to the reflux of bile and is not an ideal reconstruction method. Bile duct alternatives for bile duct defects have not been developed for over 100 years. In the present situation where the wound healing of the bile duct defect cannot be controlled, only the use of a bioabsorbable material, such as a scaffold, and the regeneration of the bile duct outside the scaffold can be expected as a bile duct substitute.

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INTRODUCTION

The treatment of gastrointestinal diseases in the 21st century involves robotic and endoscopic surgeries, which aim to minimize potential risks and side effects[1-3]. Minimally invasive endoscopic treatments have been developed to facilitate functional preservation[4,5]. For diseases of the biliary system, the use of laparoscopic cholecystectomy as a treatment for cholelithiasis has become widespread, and minimally invasive approaches have been pursued[6]. In contrast, the incidence of severe iatrogenic extrahepatic bile duct injury due to laparoscopic cholecystectomy has increased significantly worldwide compared to that due to laparotomy surgery[7]. With regard to bile duct injuries, there is currently no bile duct substitute (BDS) for partially defective or damaged parts of the bile duct. Reconstruction by anastomosis of the hepatic bile duct and intestine is typically performed[8].

Bile duct-intestinal anastomosis is a biliary tract reconstruction procedure that was first performed by von Winiwater in 1880[9]. However, liver abscess, cirrhosis, and liver dysfunction were often observed in patients who underwent this anastomosis. In the early 20th century, retrograde cholangitis tended to cause chronic inflammation if duodenal papilla function was not preserved[10,11]. The suboptimal nature of this approach resulted in attempts to preserve papilla function and to develop alternatives for addressing bile duct defects and injury. Chronic inflammation caused by abnormal pancreatic-bile duct junctions, intrahepatic stones[12,13], and exposure to organic solvents from the printing industry is considered a high-risk factor for cholangiocarcinoma[14]. Therefore, the development of BDS has emerged as a critical, unmet need. To date, various alternatives, including autologous tissue[10,15-18], non-bioabsorbable[19-23], bioabsorbable materials[24-28], and decellularized tissue[29,30], have been investigated. Nevertheless, BDSs with widespread clinical applications have not yet been developed. In this review, we discuss potential factors underpinning the failure to develop clinically usable products despite efforts to develop BDSs for more than a century. Furthermore, we highlight the types of BDSs that may be clinically applied in the near future.

MATERIALS AND METHODS

We searched the PubMed electronic database to identify studies conducted to develop bile duct alternatives until December 2021 and identified studies in English. The following search items for the data relevant to "why has a product that can replace bile ducts not been developed?" were included: "bile duct alternative", "bile duct substitute", "bile duct regeneration", "biliary alternative", "extrahepatic bile duct", "biliary regeneration", and "bile duct reconstruction". Studies using large animals such as dogs, pigs, and goats were included, whereas studies using small animals such as rats and mice were excluded. To evaluate the efficacy of the BDS, the "type of substitute", "shape and length of substitute", "method of reconstruction of the bile duct by substitute", and "observation period" were included as search terms. The items to be examined were "presence or absence of regeneration process", "localization of regenerated bile duct to substitute", "number of large animals that could be sacrificed and killed intentionally", and "cause of narrowing of substitute". We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

For studies in which the items could be determined from the abstract or text, the number of experimental large animals used was eight or more. The full text was reviewed by two researchers (Miyazawa M, Takashima J). In each of these studies, the cases in which BDS transplantation was successful were as follows: These cases were sacrificed as planned before BDS transplantation, no stenosis was observed at the anastomotic site between the BDS transplantation site and the natural bile duct, and there was no

liver dysfunction after BDS transplantation.

Animal type

In small animals, such as rats, jaundice is unlikely to occur even if the extrahepatic bile duct is narrowed, and liver dysfunction may be difficult to evaluate. As such, BDS transplantation may be difficult[31]. Accordingly, only large-animal studies were considered.

Size of BDS

If the length of the BDS implantation segment was less than 1 cm, tissues such as the omentum may migrate around it after inserting the T-tube into the defective bile duct segment[32]. Therefore, BDSs ≤ 1 cm and > 1 cm in length were considered separately. For the same reason, patch-like or circular implantation of the BDS was examined separately. Regarding the implantation method, the site of BDS implantation (between the common bile duct or between the common bile duct and intestine) was examined separately because it affects the patency of the BDS lumen.

Observation period after BDS implantation

Early after BDS transplantation, stenosis of the BDS may not occur in the event of retrograde cholangitis or severe inflammation at the alternative transplant site. After chronic inflammation, the bile duct becomes narrowed due to the gradual hyperplasia of connective tissue around the substitute[33]. After stent insertion into the BDS, bile may flow through the stent and a bile plug may not be formed in the BDS in the early stage of BDS transplantation[34]. As anastomotic stenosis was considered less likely to occur when a stent was inserted, the observation period after BDS transplantation was included in the examination items.

Bile duct regeneration

After the formation of connective tissue in the shape of the bile duct, the BDS lumen does not become completely stenotic early after BDS transplantation, even if bile duct regeneration does not occur and bile remains in the lumen. However, stenosis tends to occur after a prolonged period[35]. Tissue regeneration in the defective bile duct area occurs due to wound healing[35]. The mature bile duct takes time (3 mo or more) to regenerate from bile duct stem cells[25,36,37] (Figure 1). Therefore, to examine the effectiveness of BDS for inducing bile duct regeneration, histological images of bile duct regeneration at the BDS transplantation site were included in the examination. If the study did not report neo-bile duct regeneration and the histology was similar to that of the native bile duct, the tissue was excluded from evaluation. The histology of the anastomotic site between the BDS and native bile duct was examined because the bile duct epithelium is continuous at the anastomotic site if stenosis of the anastomotic site does not occur[38].

Localization of bile duct regeneration with respect to BDS implants

We did not identify any reports of bile duct regeneration on the inner surface of the T-tube when it was placed in the injured part of the bile duct. This suggests that the bile duct does not regenerate on the inner surface of non-bioabsorbable BDSs. However, it is important from the viewpoint of wound healing whether the localization of the regenerated bile duct is the outer surface of the BDS, the part of the BDS itself, or the inner surface of the BDS (only the bile passage surface). For these reasons, the site where the regenerated bile duct regenerates was included in the examination items for the BDS transplantation site. When the localization of bile duct regeneration was not specified, it was judged from the BDS implantation site and bile passage position in the paper.

Causes of stenosis

Narrowing of the anastomotic site between the BDS and the native bile duct or the BDS lumen was evaluated as a separate cause of wound healing. We also examined the stenotic tissue type. For BDS lumen and anastomotic site stenosis, scar contraction was considered to occur over a prolonged period if granulation or connective tissue growth was reported[35,39,40].

BDS REPORTED TO DATE

The literature search enabled the classification of BDSs into four categories: Autologous tissues[10,15-18], non-bioabsorbable materials[19-23], bioabsorbable materials[24-28], and others (decellularized tissues[29,30], structures made with 3D printers[41,42], *etc.*).

BDS using autologous tissue

Tissues with a similar morphology to that of the extrahepatic bile duct and lumen have been investigated as BDSs. In practice, arteries[43], veins[15,17-19,44], ureters[45], skin[46], and jejunum[16] have been used as grafts. Due to the thickness of the extrahepatic bile duct and wall, the femoral vein was

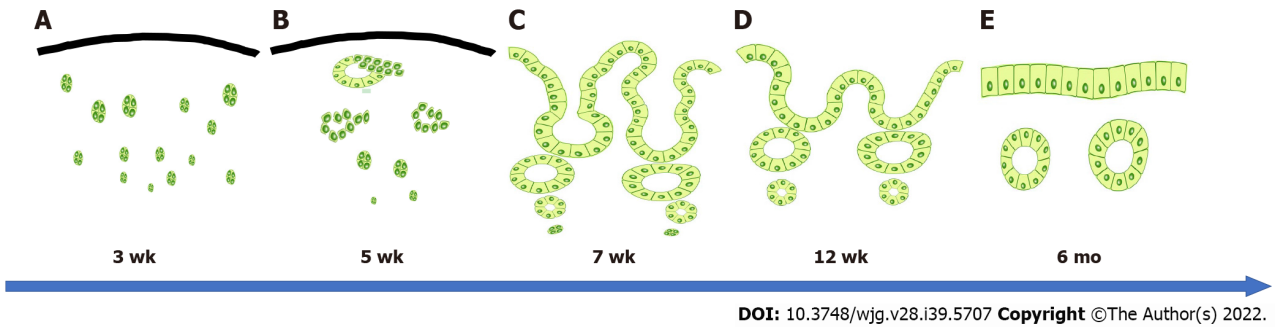

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Figure 1 Ideal bile duct regeneration process. A: Bile duct regeneration at approximately 3 wk. Numerous cell masses appear in the stroma that are thought to form peribiliary glands; B: Bile duct regeneration at approximately 5 wk. A ring-shaped peribiliary gland-like structure is observed, in which cell masses that are thought to form peribiliary glands are fused; C: Bile duct regeneration at approximately 7 wk. Numerous bile duct-attached glandular structures are observed on the bile passage surface, and the epithelial surface exhibits a high papillary morphology; D: Bile duct regeneration at approximately 12 wk. The number of peribiliary glands on the bile passage surface is decreased, the peribiliary glands become fused, and the epithelial surface becomes more even; E: Approximately 6 mo after bile duct regeneration. Similar to the native bile duct, the epithelial surface becomes a single layer of cubic columnar epithelium.

often used. In BDSs using these autologous tissues, necrosis of the substitute in the early stage of transplantation and obstruction due to attachment of the bile plug to the substitute in the middle stage of transplantation were common[10,17,18,44,47]. In the long term, scar contraction occurs due to the growth of connective tissue around the substitute and at the anastomotic site[10,17-19,44]. To address these issues, attempts have been made to wrap the omentum around the substitute to supply blood flow or to use stents and cuffs to prevent obstruction of the BDS lumen and anastomotic site[17,48,49]. As the BDS did not regenerate to the extent of the native bile duct, few BDSs were successful, and no clinically usable product was developed[48,49]. The localization of neo-bile ducts to the BDS, which attempted to promote bile duct regeneration, formed a part of the autologous tissue itself.

The most commonly used species in these studies was dog. Pearce *et al*[10] investigated autologous alternative veins as a BDS and concluded that 1 in 32 successful cases over 3 mo was insufficient for the use of autologous tissue as a BDS. A study by Dunphy and Stephens[19] using large animals (44 sheep and 8 pigs) evaluated autologous arteries, veins, and homozygous arteries. Only sheep that received autologous arteries as a BDS survived for 6 mo or more, but bile duct dilation on the liver side was observed. Myers *et al*[18] conducted a circular transplantation experiment using autologous bile ducts, arteries, veins, and genomic grafts to treat bile duct defects in 28 dogs. All homografts were rejected, and the dogs that received transplants died within 13 d.

Even in transplantations using autologous tissue, histological assessment revealed that the bile duct epithelium did not regenerate on the epithelial surface, fibrous connective tissue was increased on the epithelial surface, and the BDS transplantation site became stenotic. The authors concluded that self-organization is not possible in BDS. In 2009, Palmes *et al*[48] reported a high success rate of transplantation of the external jugular vein and a bioabsorbable stent as a BDS in pigs. However, histological changes in the bile ducts of autologous veins have not been reported (Table 1).

Due to the lack of blood supply in autologous tissue BDSs, the tissue becomes necrotic, and the anastomotic site is scar-contracted. A BDS capable of allowing bile to flow freely into the duodenum over a prolonged period has not yet been developed. It is unlikely that autologous tissue will resemble the native bile duct in the context of wound healing[40,50,51]. Stenting through the anastomotic site was effective in preventing narrowing[17,48,49]. High success rates have been reported when bioabsorbable stents are placed in the venous lumen; however, it is unclear how autologous venous tissue is induced for good bile duct regeneration. These findings suggested that autologous tissue cannot be used as a BDS.

BDS using non-bioabsorbable material

Since the 1930s, polyvinyl sponge[20], polytetrafluorethylene[22,23], Teflon[19,52], Dacron[53], and polyethylene[54,55] have been used as non-bioabsorbable BDS materials. These alternatives were used experimentally as patches or rings, but most studies reported high rejection rates early in transplantation and varying degrees of cholangitis, narrowing of the alternative lumen, and stenosis of the anastomotic site with the native bile duct[19,27,28]. Although partial success has been reported, the bile duct epithelium failed to regenerate on either the medial side (bile passage surface) or lateral side of these alternatives[29,30]. As a result, the perimeter of these BDSs was covered with fibrous connective tissue, and the luminal surface was clogged with bile plugs[19-22]. This resulted in stenosis of the anastomosis with the native bile duct, which prevented bile passage. As such, research on cyclic BDS made solely from non-bioabsorbable materials has ceased.

Sherman *et al*[21] transplanted a BDS made from acrylamide into dogs. In the stented group, 7 of the 33 cases were successful over 3 mo. However, bile duct regeneration has not been reported. Bergan *et al*

Table 1 Bile duct substitute using autologous tissue

Ref.	Journal	Substitute (*n*)	Stent (*n*)	Animal type (*n*)	Size of BDS (cm)	Method of reconstruction of bile duct by BDS (*n*)	Observation period after implantation	Localization of regenerated bile duct	Causes of stenosis	Note (planned sacrificial death and epithelialization)
Shea and Hubay[15], 1948	*Ann Surg*	Femoral vein (21)	Vitallium tube	Dog (21)	Ring (1.5)	CBC (21)	Maximum 208 d	BDS itself	Necrosis of BDS itself, narrowing of the BDS lumen, and narrowing of the anastomosis with the native bile duct	Although 14 out of 21 dogs were intentionally killed, the tissue of the regenerated bile duct was shown only as a result, and the process of bile duct regeneration was not demonstrated
Kirby and Fitts[16], 1950	*Arch Surg* (1920)	Jejunum (9)	T-tube	Dog (9)	Jejunum (2.5)	GBC (5); CBC (4)	Maximum 13 mo	BDS itself	BDS stenosis was not observed when the T-tube was inserted	Seven out of nine dogs were intentionally killed; however, no epithelial regeneration was observed at the anastomotic site. The procedure was too complicated
Pearce *et al* [10], 1951	*Ann Surg*	Femoral vein (32)	Lord and blakemore tube	Dog (32)	Ring (1.0)	CBC (10); CBJ (20); GBC (2)	Maximum 6 mo	BDS itself	Necrosis of autologous tissue, narrowing of the lumen of autologous tissue, narrowing of the anastomosis with the native bile duct, necrosis of BDS itself, narrowing of the BDS lumen, and narrowing of the anastomosis with the native bile duct	Only 1 of the 32 dogs survived for more than 6 mo. It was investigated in 32 dogs; however, in the end, fibrosis of the vein and stenosis of the anastomotic site with the native site occurred, and bile duct epithelial regeneration was not observed. It was concluded that the vein was not suitable for BDS
Ulin *et al* [17], 1955	*Ann Surg*	Vascularised jugular vein (10)	Polyethylene tube	Dog (10)	Ring (2.0-5.0)	CBC (10)	Maximum 10 mo	BDS itself	Necrosis of autologous tissue, narrowing of the lumen of autologous tissue, narrowing of the anastomosis with the native bile duct, necrosis of BDS itself, narrowing of the lumen of BDS, and narrowing of the anastomosis with the native bile duct	The omentum was used to maintain blood flow to the BDS, but in some cases, it functioned as a BDS only during the period when the stent was in place (6 out of 10 dogs). Bile duct regeneration process was not studied. No regeneration of the bile duct epithelium was observed
Myers *et al* [18], 1960	*Ann Surg*	Femoral vein and artery, bile duct (17), and homologous bile duct (6)	Polyethylene tube	Dog (28)	Ring (unknown)	CBC (23)	Maximum 449 d	BDS itself	Necrosis of autologous tissue, narrowing of the lumen of autologous tissue, narrowing of the anastomosis with the native bile duct, necrosis of BDS itself, narrowing of the BDS lumen, and narrowing of the anastomosis with the native bile duct	BDS using autologous veins, arteries, or allogeneic arteries also narrowed shortly after transplantation. No bile duct epithelial regeneration was observed
Dunphy and Stephens [19], 1962	*Ann Surg*	Autologous vein and artery (20), and homologous artery (32)	T-tube	Goat (44), dog (8)	Ring (1.0)	CBC (52)	Maximum 9 mo	BDS itself	Necrosis of autologous tissue, narrowing of the lumen of autologous tissue, narrowing of the anastomosis with the native bile duct, necrosis of BDS itself, narrowing of the BDS lumen, and narrowing of the anastomosis	In an experiment using autologous veins and T-tube as BDS, 2 dogs survived for more than 6 mo; however, both dogs demonstrated dilation of the bile duct on the liver side. No bile duct epithelial regeneration was observed

									with the native bile duct	
Belzer *et al* [44], 1965	*Ann Surg*	Femoral vein (20)	T-tube	Goat (20)	Patch (3.0-4.0)	Patch (20)	Maximum 11 mo	BDS itself	Necrosis of autologous tissue, narrowing of the lumen of autologous tissue, narrowing of the anastomosis with the native bile duct, necrosis of BDS itself, narrowing of the BDS lumen, and narrowing of the anastomosis with the native bile duct	Only 3 out of 20 dogs were intentionally killed, but no good bile duct epithelial regeneration was observed
Lindenauer and Child [47], 1966	*Ann Surg*	Vascularized jugular vein (14)	(-)	Dog (14)	Ring (unknown)	CBC (14)	Maximum 18 mo	BDS itself	The omentum increased blood flow to the BDS; however, it resulted in scar contraction. Necrosis of BDS itself, narrowing of the BDS lumen, and narrowing of the anastomosis with the native bile duct	No dog survived for more than 3.5 mo, although the omentum was used to maintain BDS blood flow
Palmes *et al* [48], 2009	*J Invest Surg*	External jugular vein (18)	PLA stent (12)	Pig (18)	Ring (2.0)	CBC (18)	Maximum 6 mo	BDS itself	When the stent was not inserted, the BDS was necrotic. When the stent was inserted, the BDS lumen was preserved, but eventually, it became necrotic and narrowed	Of the 18 dogs, all 12 stented dogs were deliberately killed. However, the process of regeneration of veins into the bile duct was not reported
Liang *et al* [49], 2012	*World J Gastroenterol*	Omentum (8)	Bioabsorbable stent	Pig (8)	Ring (0.5-1.0)	CBC (8)	Maximum 4 mo	BDS itself	The BDS lumen was preserved when the stent was inserted	The bile duct defect was repaired with an omentum, which was similar to inserting a T-tube into the defect. Bile duct regeneration was also poorly demonstrated

BDS: Bile duct substitute; CBC: Common bile duct to bile duct substitute to common bile duct; CBJ: Common bile duct to bile duct substitute to jejunum; GBC: Gallbladder to bile duct substitute to common bile duct; PLA: Polylactide acid.

[20] attached blood vessels to a BDS composed of polyvinyl sponge in dogs. Of the 12 dogs examined, 4 survived for more than 60 d, but the transplant was ultimately unsuccessful due to the formation of bile plugs inside the substitute. Dunphy and Stephens[19] examined Teflon as a BDS in four dogs and four sheep, but all failed because of severe rejection early in the transplantation. Recently, Gómez *et al*[23] investigated Gore-Tex as a BDS in 12 dogs and reported that 11 cases were successful. However, BDS was surrounded by strong fibrotic tissue and exhibited narrowing, indicating that it was not clinically usable in the long term (Table 2).

Currently, cyclic non-absorbable materials, such as polytetrafluoroethylene, are used clinically as artificial blood vessels. Anticoagulants are used to prevent blood from coagulating in artificial blood vessels when the blood vessel diameter is small[56]. Compared to blood, bile is more viscous and has a slower flow velocity. The bile duct diameter is similar to that of small blood vessels[57]. As such, this material may be unsuitable because the BDS lumen may be blocked by a bile plug[21,22]. In addition, the epithelium does not regenerate continuously at the anastomotic site between the BDS and native bile duct, scar contraction occurs in the long term after transplantation[38]. A bile plug may form if a tubular stent is inserted to secure bile passage, even when using non-bioabsorbable materials. This phenomenon

Table 2 Bile duct substitute using non-bioabsorbable material

Ref.	Journal	Substitute (*n*)	Stent	Animal type (*n*)	Size of BDS (cm)	Method of reconstruction of bile duct by BDS (*n*)	Observation period after implantation	Localization of regenerated bile duct	Causes of stenosis	Note (planned sacrificial death and epithelialization)
Dunphy and Stephens[19], 1962	*Ann Surg*	Teflon (8)	(-)	Dog (4), goat (4)	Ring (1.0)	CBC (8)	Maximum 7 wk	BDS outside	Narrowing of the anastomosis with the native bile duct; narrowing of the lumen of BDS	In all cases, the hepatobiliary enzyme levels increased, and no survivors were observed for more than 7 wk after transplantation
Bergan *et al*[20], 1962	*Arch Surg*	Vascularized polyvinyl sponge (21)	(-)	Dog (21)	Ring (0.5)	CBC (21)	Maximum 14 mo	BDS outside	Narrowing of the anastomosis with the native bile duct; narrowing of the lumen of BDS	Four out of 21 dogs survived for > 60 d after transplantation, and four of them had stenosis of BDS
Sherman *et al* [21], 1963	*Ann Surg*	Acrylamide with Dacron (33)	(-)	Dog (33)	Ring (1.5-3.5)	CBC (33)	Maximum 31 mo	BDS outside	Narrowing of the anastomosis with the native bile duct; narrowing of the lumen of BDS	Twenty-six out of 33 dogs died within 3 mo. In all cases, fibrotic thickening around the BDS and severe scar contraction had occurred at the site of anastomosis
Mendelowitz *et al*[22], 1982	*Am J Surg*	Gore-Tex (6), dacron (2)	(-)	Dog (8)	Ring (2.0-3.0), patch (2.0 cm × 1.0 cm)	Patch (Gore-Tex) (2), CBJ (Gore-Tex) (2), CBC (Gore-Tex) (1), CBC (Dacron) (2), GBJ (Gore-Tex) (1)	Maximum 40 d	BDS outside	Narrowing of the anastomosis with the native bile duct; narrowing of the lumen of BDS	In all cases, a bile plug was found in the lumen of the BDS, and a high degree of fibrotic thickening was found around the site of anastomosis
Gómez *et al*[23], 2002	*J Gastrointest Surg*	Gore-Tex (12)	(-)	Dog (12)	Ring (2.0-3.0)	CBC (12)	Maximum 3 mo	BDS outside	Narrowing of the lumen of BDS	Eleven out of 12 dogs were intentionally killed, but severe fibrotic thickening was observed around the BDS

BDS: Bile duct substitute; CBC: Common bile duct to bile duct substitute to common bile duct; CBJ: Common bile duct to bile duct substitute to jejunum; GBJ: Gallbladder to bile duct substitute to jejunum.

is similar to current endoscopic stenting for bile duct stenosis[58,59].

BDS using bioabsorbable material

Due to the failure to develop clinically applicable BDSs made from autologous tissue or non-bioabsorbable materials, increasing focus has been placed on bioabsorbable materials as BDSs. This concept is based on the technique of tissue engineering proposed by Langer and Vacanti[60] in 1993 for bile duct regeneration. The complex formed by the bioabsorbable material and cells attached to the material is absorbed in the body while the bioabsorbable material acts as a scaffold to maintain the environment and shape of the organ[60,61]. Concurrently, the cells attached to the scaffold regenerate the target organ. Natural polymers (particularly collagen)[24,27,28] and engineered synthetic polymers [25,26,62-64] have been investigated as BDSs based on bioabsorbable materials.

BDS using natural polymers

Alternative natural polymers to collagen have been investigated, such as the small intestinal submucosa (SIS) using porcine submucosa. Using this SIS, Rosen *et al*[24] reported that 9 cases of patch-like transplantation and 6 cases of circular transplantation were performed as BDS, and 13 of them were successful. However, bile duct regeneration was not observed as a pathological finding. On the other hand, in another study using SIS as a BDS, scar contraction was high[65]. As such, this material has not been clinically applied as a BDS (Table 3).

Nakashima *et al*[66] reported the successful use of collagen as a BDS in consideration of cell adhesion. However, collagen was attached to a non-bioabsorbable material (polypropylene) to maintain the hardness of this BDS; therefore, it may not be a strictly bioabsorbable BDS. The BDS scaffold was sutured to the native bile duct. As bile passes through the lumen, the scaffold must maintain an annular shape and therefore a degree of hardness. Collagen tends to lose its shape when immersed in water[66, 67]. Collagen-based BDSs require hardness in other substances to maintain the scaffold hardness, resulting in an absorption period longer than several months. For this reason, SIS uses collagen and submucosal tissue to maintain hardness[24].

To promote bile duct regeneration within the bioabsorbable material itself, the period of *in vivo* absorption of the bioabsorbable material is important for suppressing scar contraction. In the case of artificial skin using collagen for skin regeneration, it has been reported that the half-life of the bioabsorbable material, which most strongly suppresses scar contraction, is approximately 14 d[67]. If a BDS made of a bioabsorbable material has a half-life of 3-4 wk or more, scar contraction may be high. When bioabsorbable materials other than the skin are used as alternatives for bile duct regeneration, the absorption period of such materials must also be considered, but this is not the case for SIS[24].

In collagen-based BDSs, the density of the material ligand is important for cell adhesion to promote bile duct regeneration[68]. However, there is a paucity of research in this area. If attempts are made for bile duct regeneration within the bioabsorbable material itself, scar contraction of the BDS part cannot be suppressed after transplantation unless these points are taken into consideration.

BDS using synthetic polymers

BDSs based on synthetic polymers are predominantly composed of polyglycolic acid (PGA)[26] and polycaprolactone[24,62], BDSs produced using PGA fibers may fail to maintain their radial shape. In many studies, the major axis of the bile duct has been replaced by approximately 1 cm. The absorption period of PGA is approximately 3 mo; as such, chronic inflammation occurs, and bile duct regeneration occurs at the implanted site. As such, attempts to regenerate the bile duct epithelium on the inner surface (bile passage surface) of this BDS eventually cause scar contraction similar to that of non-bioabsorbable BDS, and previous efforts have been unsuccessful[24,61].

Studies employing polycaprolactone-based BDSs have reported good bile duct regeneration outside the BDS implant. The material in these studies comprised a 50:50 copolymer of lactic acid and caprolactone, which was reinforced with latticed PGA fibers to facilitate suturing[25]. Generally, the absorption period is 6-8 wk, and the material becomes vulnerable *in vivo* for approximately 3 wk. After the BDS becomes fragile and sheds into the duodenum, a bile duct thicker than the outer circumference of the BDS regenerates outside the BDS. Cells migrating to the BDS as a foreign body reaction may promote bile duct regeneration[25]. Previous studies have reported good results, including BDS experiments in infectious reservoirs[69]. The occurrence of bile duct regeneration on the outside of the BDS resembles bile duct regeneration after insertion of a T-tube into a defective bile duct followed by T-tube removal (Table 3).

As BDSs using synthetic polymers can be engineered, the period of absorption in the body can be adjusted[70]. However, if the BDS is hard to maintain the shape of the bile duct, the absorption period may be prolonged. As BDS results in longer chronic inflammation due to a foreign body reaction, the results are likely to be similar to those of non-bioabsorbable materials. In contrast, if the absorption period is too short, the BDS transplantation site becomes fragile and is destroyed after transplantation. Bile may flow out of the BDS transplantation site, making this material unsuitable for BDS. With regard to cell adhesion, the scaffold itself (for example, PGA only) has lower cell adhesion compared to collagen-based scaffolds owing to the lack of receptors for cell adhesion[38]. Therefore, to regenerate the scaffold itself within the bile duct, materials in which receptors are added to the scaffold have been investigated[38]. Failure of the bile duct to regenerate in the scaffold part while being absorbed prevents clinical application as a BDS; hence, these materials remain in the development stage.

BDS made of other materials

In recent years, attempts have been made to utilize decellularized tissues as BDSs because of the lack of an immune reaction when transplanted into a living organism[29,30]. The use of decellularized tissues as scaffolds for liver regeneration has been investigated. The bile was reported to drain into the duodenum as a tube for a prolonged period and functioned while the stent was inserted. However, reports of long-term bile duct regeneration and function after stent removal are lacking.

Scaffolds of the same shape as that of the extrahepatic bile duct have been produced using 3D printing[41,42]. The extrahepatic bile duct has been reported to regenerate in a ring shape, but no

Table 3 Bile duct substitute using bioabsorbable material

Ref.	Journal	Substitute	Stent	Animal type (*n*)	Size of BDS (cm)	Method of reconstruction of bile duct by BDS (*n*)	Observation period after implantation	Localization of regenerated bile duct	Causes of stenosis	Note (planned sacrificial death and epithelialization)
Rosen *et al* [24], 2002	*Surgery*	SIS	(-)	Dog (15)	Patch: (2.0 cm × 1.0 cm), ring: (2.0-3.0)	Patch (9), CBC (6)	Maximum 5 mo	BDS itself	Scar contraction at the site of anastomosis on the duodenal side	Thirteen out of 15 dogs were intentionally killed. The regenerated bile duct tissue was shown consequently, and the process of regenerating the bile duct was not shown
Miyazawa *et al*[25], 2005	*Am J Transplant*	P (CL/LLA) with PGA	(-)	Pig (18)	Ring (3.0)	CBJ (18)	Maximum 6 mo	BDS outside	No narrowed BDS	All pigs were intentionally killed. A good bile duct regeneration process was shown
Nau *et al* [26], 2011	*HPB (Oxford)*	PGA and TMC	5 Fr pancreatic stent	Dog (11)	Ring (1.0)	CBC (11)	Maximum 12 mo	BDS itself	Narrowing of the BDS lumen	Ten out of 11 dogs were intentionally killed. No good bile duct epithelial regeneration was observed
Li *et al*[27], 2012	*Biomaterials*	Collagen with bFGF	(-)	Pig (26)	Patch (2.0 cm × 1.0 cm)	Patch (26)	Maximum 6 mo	BDS itself	No narrowed BDS	All pigs were intentionally killed. The regenerated bile duct tissue was shown consequently, while the process of regenerating the bile duct was not shown
Tao *et al*[28], 2015	*Artif Organs*	Collagen	Plastic stent	Pig (20)	Patch (2.0 cm × 0.6 cm)	Patch (12)	Maximum 12 wk	BDS itself	No narrowed BDS	All pigs were intentionally killed. The regenerated bile duct tissue was observed consequently, while the process of regenerating the bile duct was not shown
Tanimoto *et al*[62], 2016	*Langenbecks Arch Surg*	P (CL/LLA)	T-tube	Pig (11)	Ring (2.0)	CBC (11)	Maximum 6 mo	BDS itself	No narrowed BDS	All pigs were intentionally killed. A high degree of fibrosis was observed in the regenerated bile duct tissue
de Abreu *et al*[63], 2020	*J Biomater Appl*	Bacterial cellulose film	T-tube	Pig (10)	Patch (2.0 cm × 1.0 cm)	CBC (20)	Maximum 330 d	BDS itself	No narrowed BDS	All pigs were intentionally killed. No process of bile duct regeneration was shown

BDS: Bile duct substitute; bFGF: Basic fibroblast growth factor; CBC: Common bile duct to bile duct substitute to common bile duct; CBJ: Common bile duct to bile duct substitute to jejunum; P(CL/LLA): Polyε-caprolactone/poly l-lactide; PGA: Polyglycolic acid; SIS: Small intestinal submucosa; TMC: Trimethylene carbonate.

studies to date have examined bile duct regeneration using these BDSs. Furthermore, there have been efforts to develop an actual bile duct as an organoid *in vitro* for transplantation[70]. However, it has not been possible to produce organoids of a certain length in the longitudinal direction for clinical use and with a length that can be sutured.

FACTORS TO CONSIDER FOR BDS DEVELOPMENT

Below, we discuss the factors that should be considered in the development of clinically applicable BDSs.

Bile duct wound healing

Bile duct regeneration must occur concurrently with wound healing[40,50,51]. Notably, the natural course of wound healing involves scar contraction. Therefore, if the BDS does not reduce scar contraction, the migrating cell mass results in scar contraction and lumen narrowing after removal of the BDS or decomposition and absorption[35,51]. For the BDS to promote bile duct regeneration, the BDS implant must be guided into the regeneration process while maintaining the shape of the bile duct rather than increasing scarring of the cell mass[40]. As such, which allows the cell mass that regenerates the bile duct to maintain the shape of the bile duct when the BDS is absorbed or removed.

A BDS made of a non-bioabsorbable material that has been present in the body for a prolonged period retains its shape until the BDS is removed, but the lumen is prone to clogging by bile plugs[20-22]. Further, the anastomotic site with the native bile duct will be narrowed due to connective tissue growth[50,51]. Current bile duct regeneration methods using BDSs suggest that after the cell mass gathers around the foreign body and the BDS forms the shape of the bile duct, the cell mass regenerates as a bile duct after BDS removal[25]. If the BDS cannot maintain the shape of the bile duct, a stent may be used instead.

Studies have demonstrated that bone marrow-derived and adipose-derived cells are effective in suppressing scar contraction[72,73]. In addition, it has been reported that fibrosis is suppressed by controlling the function of macrophages that have migrated to the injured region during the remodeling period of wound healing[40,51]. However, methods for reliably suppressing scar contraction have yet to be developed[72,73]. For bile duct regeneration and retention of normal tissue structure, it is necessary for the dynamics and function of multiple types of cells that have migrated around the BDS to be tightly regulated and to reduce scar contraction.

Bile properties

Compared to blood, bile is more viscous and has a slower velocity[57]. If a BDS is not absorbed in the body, a bile plug may adhere to the BDS at the anastomosis site with the lumen or native bile duct. This results in impaired bile flow and narrowing of the lumen. In studies using Teflon (a non-bioabsorbable material) as a BDS, anticoagulants are often used even for blood. Therefore, further measures are required to prevent bile plug formation. This resembles the insertion of metal or tube stents for the treatment of bile duct stenosis, which often clogs the stent with a bile plug[58,59].

Bile duct regeneration

The extrahepatic bile duct is a component of the digestive tract, and the mature bile duct is regenerated *via* a regeneration process similar to that of the stomach and intestine[36,74,75]. In pigs, it takes approximately 6 mo for bile duct stem/progenitor cells to undergo regeneration to form a mature bile duct similar to the native bile duct. Furthermore, the bile duct epithelium is covered with a layer of cubic columnar epithelial cells[25] (Figures 1 and 2). Therefore, it is controversial in studies that do not show the process of bile duct regeneration, even if BDS transplantation is reported to be successful. For example, in the subsequent regeneration of the T-tube insertion site, the portion of the hole with the T-tube inserted reproduced well without any narrowing. This suggests that small partial bile duct regeneration often occurs without stenosis even if a patch of omentum or blood vessel is applied externally[76]. However, if bile duct defects are extensive and the BDS is placed between the native bile ducts, the cell mass must undergo substantial regeneration from the early stage of bile duct regeneration to regenerate the bile duct without stenosis. Studies have demonstrated that cells attached to the bioabsorbable material regenerate the bile ducts, but the mechanisms by which these cells undergo bile duct regeneration in the presence of the bioabsorbable material remain unclear[24].

Immature cells attached to the scaffold migrate using the scaffold of the BDS as a foreign substance [40,50]. These cell masses first form an assembly of the peribiliary gland[25,74,75]. When good bile duct regeneration is achieved approximately 2 mo after the initial stage of regeneration, a tall papillary shape is formed on the inner surface through which bile passes. In pigs, after approximately 3 mo of bile duct regeneration, these peribiliary glands fuse and the epithelial cells become shorter; within approximately 6 mo, these structures mature into bile ducts that are similar to native bile ducts (Figures 1 and 2)[25].

With regard to the mechanisms of bile duct regeneration in the injured part of the bile duct, activated bile duct cells mobilize immune cells, vascular cells, and mesenchymal cells to the inflamed region as a ductular reaction during bile duct ligation and inflammation[77]. This process is involved in regeneration of the inflamed area. Inflammation-activated bile duct cells secrete chemokines, cytokines, and angiogenic factors, which are involved in wound healing[35,50,51]. Furthermore, reactive ductal cells generated *via* complex mechanisms depend on the nature and intensity of bile duct injury[35,50,51]. However, further investigations of bile duct regeneration mechanisms in various bile duct injuries, such as circular transplantation of BDS, are required to develop effective BDSs.

Regeneration of anastomotic site

When the anastomosis between a BDS and the native bile duct is narrowed, the flow of bile into the duodenum is obstructed, which limits the clinical application of the BDS. In a normal gastrointestinal anastomosis, a large anastomotic hole and fixed shape that does not experience deformation are

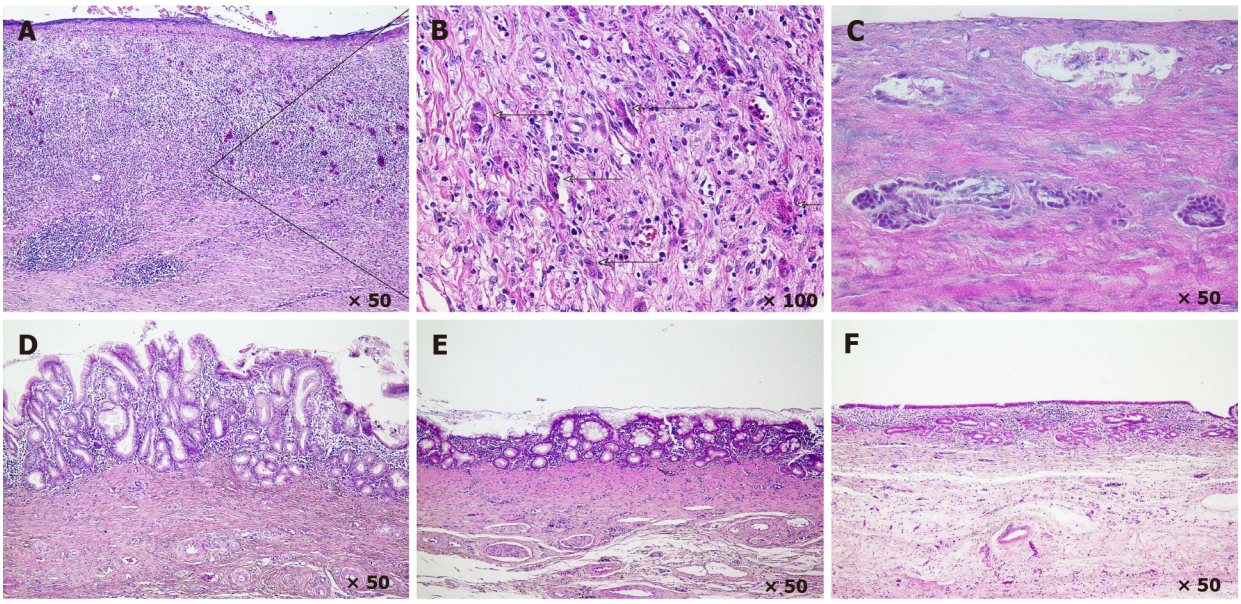

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Figure 2 Histology of bile duct regeneration on the outside of the short-term absorption type bile duct substitute. A and B: At 3 wk after bile duct substitute (BDS) implantation, a cell population in the stroma that may comprise the origin of the peribiliary gland is observed; C: At 5 wk after BDS implantation, a ring-shaped biliary gland-like structure is observed in which cell masses that are thought to form peribiliary glands are fused; D: At 7 wk after BDS implantation, many bile duct appendages are observed on the bile passage surface, and the epithelial surface exhibits a high papillary morphology; E: At 12 wk after BDS implantation, the number of peribiliary gland on the bile passage surface is decreased, the appendages begin to fuse, and the epithelial surface becomes more even; F: At 6 mo after BDS implantation, the epithelial surface becomes a single layer of cubic columnar epithelium, similar to the native bile duct.

prerequisites to prevent narrowing of the anastomosis[78]. Therefore, in surgical practice, a stent is inserted when the anastomotic hole is small[78]. For BDSs made from non-bioabsorbable materials, the extrahepatic bile duct is thin; hence, the anastomotic site with the native bile duct is likely to be narrowed by connective tissue in the absence of stent insertion. To prevent anastomotic stenosis between the BDS and the native bile duct, it may be necessary to insert a stent through the anastomotic site to maintain its shape. Even for BDSs made from bioabsorbable materials, it may be difficult to maintain the shape of the anastomotic site and stent insertion is recommended to prevent stenosis.

Localization of bile duct regeneration to BDS

Three regenerative localizations of the neo-bile duct with respect to the BDS have been identified: Outside the BDS, within part of the BDS itself, and inside the BDS (bile passage surface). If the BDS is present for a prolonged period, chronic inflammation will persist[50,51]. As such, it is unlikely that the cell mass that has migrated due to detection of the BDS as a foreign substance will regenerate into a structure similar to the native bile duct at the site of the BDS in the context of wound healing[20-22,51].

If the BDS is present for a prolonged period, the bile duct does not regenerate outside the BDS or as part of the BDS itself. Bile duct stem cells do not appear to adhere to the luminal surface of non-living non-absorbable materials, such as T-tubes. Given that the bile duct does not tend to narrow after T-tube removal, a cell mass that has migrated outside the BDS is formed. In the absence of BDS, the cell mass is exposed to fresh bile and regenerates as a bile duct, which may promote good bile duct regeneration at the BDS transplant site[25] (Figures 3 and 4).

The use of decellularized tissue as a BDS is thought to promote bile duct regeneration by cell adhesion to the luminal surface or inside the scaffold[29,30]. For BDSs made of bioabsorbable materials with a short absorption period, cell clusters contributing to bile duct regeneration migrate to the outside of the BDS and regenerate the bile duct. This bioabsorbable material may become fragile in approximately 3 wk and shed to the duodenal side, after which the cells surrounding the BDS regenerate the bile duct[25] (Figures 3 and 4). Although further research is needed, the extant literature suggests that the cell mass forms a ring-shaped structure more rapidly than during chronic inflammation and subsequently disappears from the site. Collectively, these findings suggest that bioabsorbable materials that induce good bile duct regeneration may be harnessed as effective BDSs.

RESEARCH LIMITATIONS

One study reported that when a stent was placed in the BDS, bile flowed through the stent for a certain period, resulting in a successful BDS. However, the study did not demonstrate bile duct regeneration.

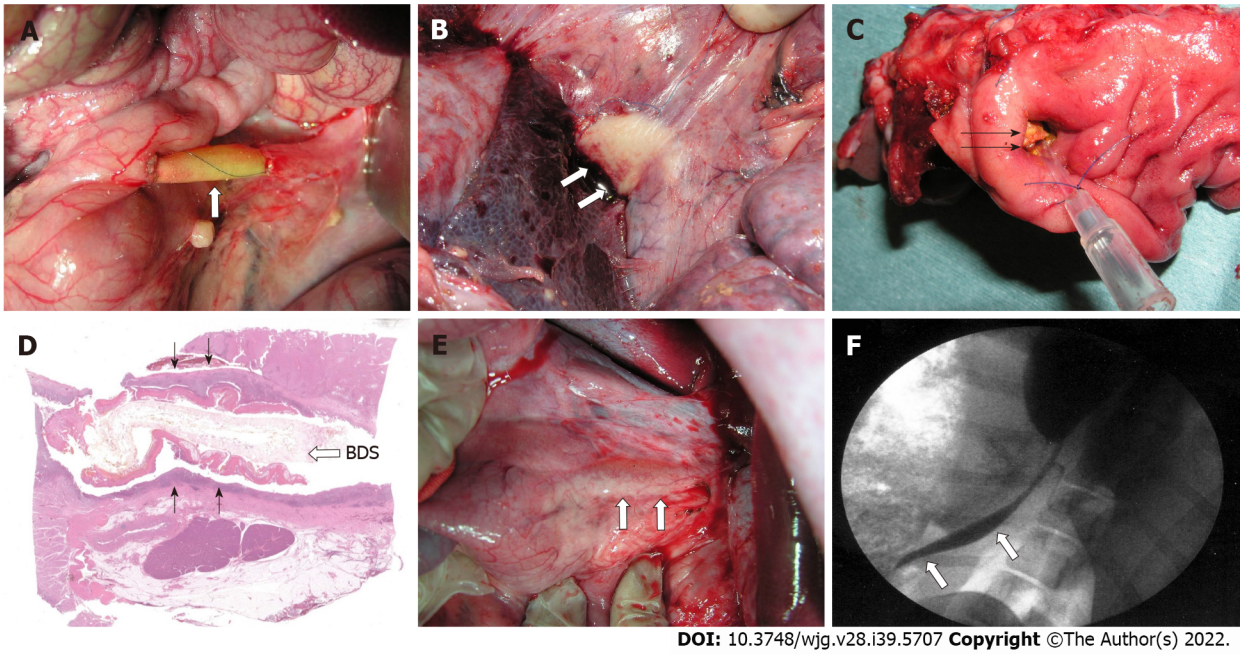

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Figure 3 Bile duct substitutes using bioabsorbable material (synthetic polymer with short absorption period). A: A bile duct substitute (BDS) using bioabsorbable material is implanted to bypass the extrahepatic bile duct (3 cm in size). Three weeks post-BDS implantation; B: White cell clusters are observed on the outside of the BDS; C: A vulnerable BDS is observed from the duodenal side; D: Dark purple connective tissue is noted on the outside of the BDS; E: At 6 mo after BDS implantation, the neo-bile duct is macroscopically similar to the natural common bile duct have been regenerated (arrow); F: Cholangiography (6 mo after BDS implantation). The BDS implant and anastomotic site become unknown, and the contrast medium flows smoothly into the duodenum (white arrows).

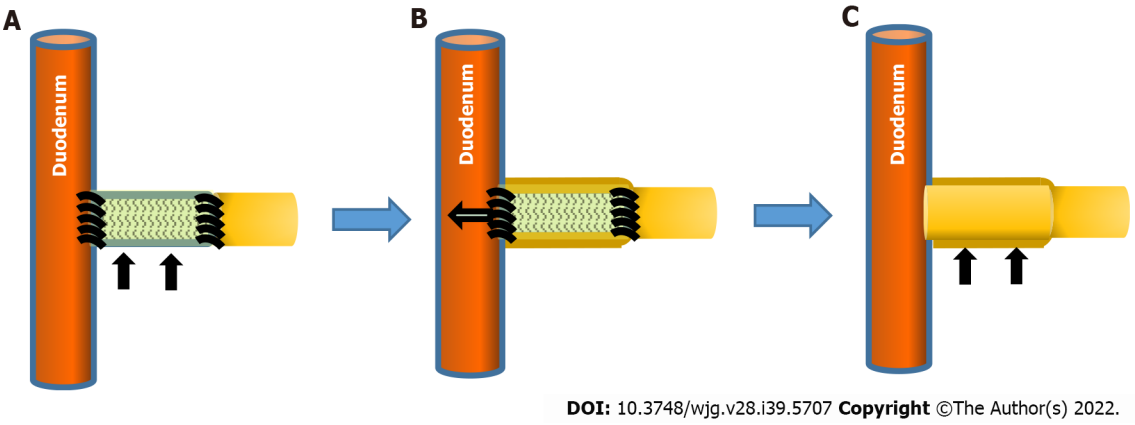

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Figure 4 Regeneration of the neo-bile duct outside the short-term absorption type bile duct substitute. A: Bile duct substitute (BDS) (black arrows) is anastomosed to the native extrahepatic bile duct; B: Immature cells attach around the BDS, forming a cylindrical cell mass outside the BDS. The bioabsorbable polymer that comprise BDS becomes fragile in the living body from approximately 3 wk and sheds to the duodenal side; C: After BDS is no longer present at the transplant site, immature cell clusters mature as bile duct cells and the bile ducts are regenerated as tissue (black arrows).

This process is similar to that of stent insertion during the treatment of benign bile duct stenosis. Nevertheless, the alternative portion eventually becomes stenotic and clinically unusable over a prolonged period. Our analysis was unable to identify these issues accurately. Although numerous studies using various BDSs have been conducted, the lack of success highlights the limitations of the field. Moreover, we did not analyze successful cases in small animals or studies using a small number of large animals.

FUTURE PERSPECTIVES

Extant research has provided novel insights into the mechanisms of repair after tissue damage[75]. If the injured area does not undergo normal repair, a high degree of fibrosis will occur in the injured area, resulting in scar formation at the site. For bile duct injuries, the injured area or the BDS implant may

become stenotic. For the regeneration of a bile duct similar to the native bile duct at the injury site, cells that have migrated to the bile duct injury site must suppress scar contraction, similar to the regeneration of other organs. In this regard, it is necessary to create a niche for bile duct regeneration similar to that of the native bile duct[73,75]. In addition, chronic inflammation is associated with prolonged and severe fibrosis, resulting in scar formation. Therefore, a BDS should not remain at the transplantation site for a prolonged period.

Based on these caveats, two methods can be considered for regenerating a bile duct similar to the native bile duct at the BDS transplantation site. The first involves the use of a short-term absorption type of bioabsorbable BDS, in which cells that have migrated to repair bile duct injury (BDS transplantation site) form the shape of the bile duct *via* a foreign body reaction. Ultimately, the BDS will no longer be present at that site and chronic inflammation does not occur (*i.e.*, the bile duct regenerates outside the BDS)[25] (Figure 4). The second method involves bile duct stem/progenitor cells adhering to part of the BDS itself, and wound healing is regulated such that bile duct regeneration progresses well while the BDS is being absorbed. Therefore, it is necessary to develop a method to control wound healing so that the scaffold portion of the decellularized tissue and adhering cells do not cause scar contraction. In summary, bioabsorbable BDSs for bile duct regeneration outside the bile duct constitute a promising development that will be clinically useful in the future.

CONCLUSION

To date, successful BDSs have not been developed. This is predominantly due to poor mechanistic understanding and lack of methods for regulating bile duct wound healing and bile duct regeneration. As an alternative to the extrahepatic bile duct, bioabsorbable materials can be used to form the shape of the bile duct, and the cell mass forming the shape of the bile duct can migrate to the external surface of this structure. Once the cell mass was able to maintain the shape of the bile duct, the BDS acting as a scaffold was removed. The development of BDSs that enable this process will permit the treatment of a wide range of bile duct defects.

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FOOTNOTES

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Country/Territory of origin: Japan

ORCID number: Mitsuo Miyazawa 0000-0002-7364-6086; Masayasu Aikawa 0000-0002-6706-8734; Junpei Takashima 0000-0002-1231-482X; Hirotoshi Kobayashi 0000-0002-4381-0439; Shunsuke Ohnishi 0000-0003-1194-4149; Yoshito Ikada 000-0002-9677-3993.

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