# Budesonide with Low-Dose 6-Mercaptopurine as a Possible New Treatment for IgG4-Related Sclerosing Cholangitis and Systemic IgG4-Related Disease: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1  **Benjamin Peter Michael Gummlich**
BC 2  **Ali Seif Amir Hosseini**
ABCDF 1  **Harald Schwörer**

1 Department of Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Center Goettingen, Goettingen, Germany
2 Department of Diagnostic and Interventional Radiology, University Medical Center Goettingen, Goettingen, Germany

Corresponding Author: Harald Schwörer, e-mail: hschwoer@med.uni-goettingen.de
Financial support: None declared
Conflict of interest: None declared

**Patient:** Male, 70-year-old
**Final Diagnosis:** Drug induced hepatopathy • gangrenous cholecystitis • IgG4 related sclerosing cholangitis • systemic IgG4 related disease
**Symptoms:** Abdominal pain • jaundice
**Medication:** —
**Clinical Procedure:** Computed tomography • magnetic resonance cholangiopancreatography
**Specialty:** Gastroenterology and Hepatology

**Objective:** Rare disease
**Background:** Systemic IgG4-related disease is a rare disease that can affect the hepatobiliary system and may lead to tissue fibrosis and organ failure. Diagnostic criteria for IgG4-related disease are well established, and systemic glucocorticoids are recommended for initiation of treatment. Besides the beneficial properties of glucocorticoids, the long-term treatment with systemic steroids carries the risk of toxicity, especially in elderly patients, in whom IgG4-related disease is more common. Furthermore, disease relapses may occur during the tapering of steroids. Overall, the optimal treatment approach for maintenance therapy has not been clarified yet and is an area of current clinical research.

**Case Report:** We present a patient with IgG4-related sclerosing cholangitis and histologically confirmed systemic (multi-organ) IgG4-related disease who was at increased risk of disease recurrence. The effects of immunosuppressants (prednisolone, 6-mercaptopurine, budesonide) on clinical symptoms, laboratory parameters (AST, ALT, AP, γGT, bilirubin), and imaging examinations (magnetic resonance cholangiography) were documented over 56 months. Control of IgG4-related sclerosing cholangitis was achieved – without systemic prednisolone – with the locally acting glucocorticoid budesonide in combination with low-dose 6-mercaptopurine. During treatment with 6-mercaptopurine, transient hepatotoxicity occurred, which was reversed by intermittent pausing and subsequent dose reduction. In addition, gangrenous cholecystitis occurred as a complication of immunosuppression and was treated by emergency cholecystectomy.

**Conclusions:** Budesonide could be a new treatment modality for IgG4-related sclerosing cholangitis. Systemic manifestations of immunoglobulin G4-related disease can be controlled with low-dose 6-mercaptopurine. Gangrenous cholecystitis may occur as a complication of immunosuppressive treatment.

**Keywords:** 6-(2,4-dinitrophenyl)mercaptopurine • Budesonide • Glucocorticoids • Immunoglobulin G4-Related Disease • Prednisolone

**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/938272

📄 3660     ▦ —     📊 2     📚 51

## Background

IgG4-related disease (IgG4-RD) is a rare disease with a local or systemic pattern of involvement [1]. Commonly affected organs are the bile ducts, pancreas, salivary glands, lymph nodes, retroperitoneum, kidneys, and the aorta [2]. IgG4-RD can present as pseudotumors and mimics, malignancies such as pancreatic cancer, cholangiocarcinoma, and lymphoma, as well as many infectious and chronic inflammatory diseases [3]. Pathognomic features include histologic findings such as lymphoplasmacytic infiltrate with increased IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis, and serum IgG4 levels may also be increased [4].

While diagnostic criteria for IgG4-RD are well established [5,6], long-term treatment regimens are not internationally standardized [7] and are an area of ongoing clinical research [8-10]. Glucocorticoids represent an important pillar of therapy [5]. Most patients with IgG4-RD are sensitive to initial glucocorticoid treatment, with response rates of up to 97-100% [7]. Response to steroids is a diagnostic criterion, but their long-term use is often limited [5]. Steroid treatment can be accompanied by serious adverse effects [11], especially in elderly patients with IgG4-RD, which limits their use for maintenance treatment [4]. Based on these findings, some patients with IG4-RD require steroid-sparing maintenance treatment to reduce glucocorticoid-related toxicity and morbidity [4].

Treatment approaches for maintenance treatment include steroids alone or in combination with immunosuppressants such as azathioprine, 6-mercaptopurine (6-MP), mycophenolate mofetil, cyclophosphamide, methotrexate, or biologicals such as rituximab [5,7,8,12]. Recent data show that a combination of glucocorticoids with additional immunosuppressants is safe and more effective than glucocorticoid monotherapy [12], induces higher remission-free and lower relapse rates, and has compatible safety profiles, compared to monotherapy with steroids, immunosuppressants, or rituximab in patients with IgG4-RD [8].

In the early period after diagnosis of IgG4-RD, mortality rates are similar to those of the general population, but in the following years, mortality may increase, with an overall mortality rate of 26.6% and a standardized mortality rate of 1.75%, especially in men [13]. Therefore, patients with IgG4-RD should receive appropriate treatment and surveillance of IgG4-RD to reduce morbidity and mortality.

## Case Report

We report a 70-year-old White male patient from Germany, who was in close follow-up for his IgG4-RD in our department.

The patient's medical history included histologically confirmed systemic IgG4-RD primarily with hepatobiliary involvement as IgG4-related sclerosing cholangitis (IgG4-SC). According to classification criteria [14], which evaluates IgG4-SC due to its pattern of involvement (proximal, distal, diffuse), our patient had type 4 IgG4-SC of the proximal bile duct, which can be difficult to differentiate from Klatskin tumor. Further typical IgG4-RD manifestations such as IgG4-related sialadenitis, IgG4-related lymphadenopathy, and focal autoimmune pancreatitis without clinical signs of pancreatitis were diagnosed in the past [15]. Other comorbidities included diabetes mellitus, arterial hypertension, and hyperlipidemia.

Our patient developed a relapse of IgG4-SC about 5 months after treatment initiation with oral prednisolone, at which time prednisolone was tapered from 10 mg to 5 mg/d. Therefore, immunosuppressive therapy was expanded to a combination of a thiopurine with prednisolone. First, azathioprine was given in combination with prednisolone for 13 months, which was replaced by 6-MP due to painful abdominal discomfort after the intake of azathioprine.

Physical examination showed a patient in good general condition, who was awake and oriented to himself, place, and time. His body mass index was 23 kg/m$^2$ (weight 61 kg, height 160 cm). The vital signs were normal and auscultation of the heart revealed no pathologic findings. Examination of the lungs showed attenuated breath sounds over the right upper lung due to a previous lobectomy for lung cancer. The other lung lobes had normal breath sounds. The bowel sounds and the liver size were normal. The Courvoisier sign was negative, and no lymph nodes, abdominal resistances, or renal angle tenderness were noted on palpation. Neurologic examination revealed paralysis of the left peripheral facial nerve, which the patient had acquired after salivary gland and lymph node resection in the past. He also had bilateral xanthelasma under his eyelids.

Regularly taken drugs were oral prednisolone (10-30 mg/d), oral 6-MP (50 mg/d), vitamin D (1000 IE/d), calcium (1250 mg/d), aspirin (100 mg/d), pantoprazole (40 mg/d), metoprolol (47.5 mg/d), subcutaneous insulin Levemir (10 IE 1-0-0), and insulin actrapid (4 IE 0-1-1).

Our patient did not take herbals or depot injections. He rarely drank alcohol and did not smoke, and he had no allergies. He received the recommended vaccinations during childhood and adulthood. He was married and had 2 children and worked as an electrician. His family history was positive for colon and stomach cancer in his father.

About 4 months after the start of 6-MP, when the dosage was increased from 50 mg/d to 75 mg/d, our patient developed increased liver parameters – ALT 155 U/L (ref. <45 U/L), AST 53 U/L
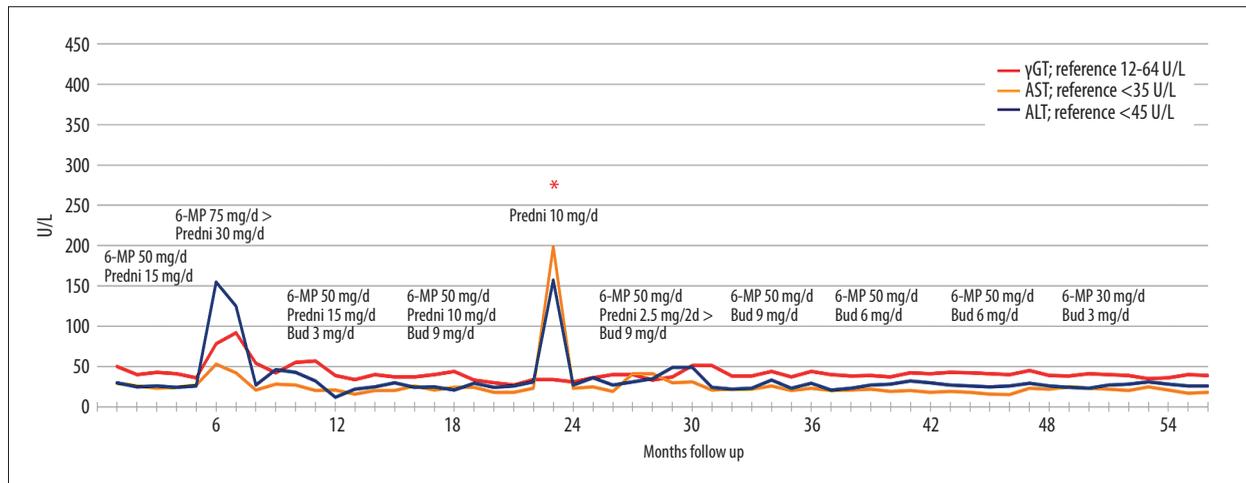
**Figure 1. Time course of AST, ALT, and γGT during follow-up.** Values of AST, ALT, and γGT are demonstrated during immunosuppressive treatments with prednisolone (Predni), 6-mercaptopurine (6-MP), and budesonide (Bud). > indicates stop of treatment. Further, gangrenous cholecystitis with cholecystectomy occurred (red star).

(ref. <35 U/L), and γGT 78 U/L (ref. <64 U/L) – suggesting drug-induced liver injury. MCV and MCH were slightly increased with 110 fl (ref. 81-95 fl) and 36.8 pg (ref. 26-32 pg), respectively. His total bilirubin, alkaline phosphatase (AP), INR, albumin, hemoglobin, and creatinine were within their normal ranges.

Despite a recommended dosage for 6-MP (max. 2.5 mg/kg body weight, adjusted for body weight, which in our patient was 152 mg/d p. o.) [16], as well as normal values for its metabolites 6-methyl-mercaptopurine (6-MMP) and 6-thioguanine nucleotides (6-TGN), 6-MP was paused and prednisolone was increased to 30 mg/d for 10 days and then quickly reduced to 20 mg/d (**Figure 1**). After that, liver enzymes (AST, ALT, γGT) normalized within the next 2 weeks, while his AP, bilirubin, and creatinine remained in normal ranges.

In the following course, 6-MP was reinitiated with a dosage of 50 mg/d p. o. (**Figure 1**), while the oral prednisolone was 15 mg/d. Furthermore, oral budesonide was added with 3 mg/d and slowly increased, reaching 9 mg/d within the next 8 weeks. Since the patient's symptoms were predominantly caused by IgG4-SC, budesonide was chosen as a locally acting steroid to target IgG4-SC in the liver. While receiving this combination of immunosuppressants, our patient was free of symptoms, his liver (AST, ALT), cholestasis (AP, γGT, bilirubin), and liver synthesis (INR, albumin) parameters remained in their normal ranges, and prednisolone was tapered again to 10 mg/d within the next 4 weeks.

About 9 weeks after the combined treatment with 6-MP (50 mg/d), prednisolone (10 mg/d), and budesonide (9 mg/d p. o.), our patient developed abdominal pain and increased liver values – AST 199 U/L (ref. <35 U/L), ALT 157 U/L (ref. <45 U/L), total bilirubin 2 mg/dL (ref. 0.3-1.2 mg/dL) – as well

as increased leukocytes 15.9 tsd/mL (ref. 4.0-11.0 tsd/mL) and CRP 310 mg/dL (ref. <5 mg/dL), while his AP and γGT and liver synthesis parameters (INR, albumin) remained in their normal ranges.

Abdominal ultrasound showed a concretion in the gallbladder but no signs of cholecystitis, and the common bile duct had a diameter of 6 mm. Due to clinically suspected cholecystitis, immunosuppressive treatments with 6-MP and budesonide were paused while prednisolone was continued at 10 mg/d. A broad-spectrum antibiotic treatment with meropenem and vancomycin was initiated and blood cultures were performed.

An abdominal CT was performed for persistent diffuse upper abdominal pain that did not respond to analgesics (novaminsulfon and piritramide). The CT scan showed signs of cholecystitis with beginning peritonitis and affection of the right colonic flexure (data not shown). Due to these findings, our patient underwent emergency cholecystectomy. Histological examinations of surgical specimens showed a perforated, acute ulcerated, phlegmonous, and necrotizing cholecystitis with local peritonitis and a cell infiltrate rich in neutrophile granulocytes but no plasma cells. Furthermore, immunohistochemical analysis of the gallbladder was negative for IgG4-RD and blood cultures for bacterial infection.

After cholecystectomy, the patient's symptoms resolved and his leucocytes, liver enzymes (including total bilirubin), and CRP normalized within a few days. Further, immunosuppressive treatments with 6-MP (25 mg/d) and budesonide (3 mg/d p. o.) were restarted in combination with prednisolone (10 mg/d). Within the next 4 weeks, doses of 6-MP were increased to 50 mg/d p. o. and budesonide to 9 mg/d p. o.
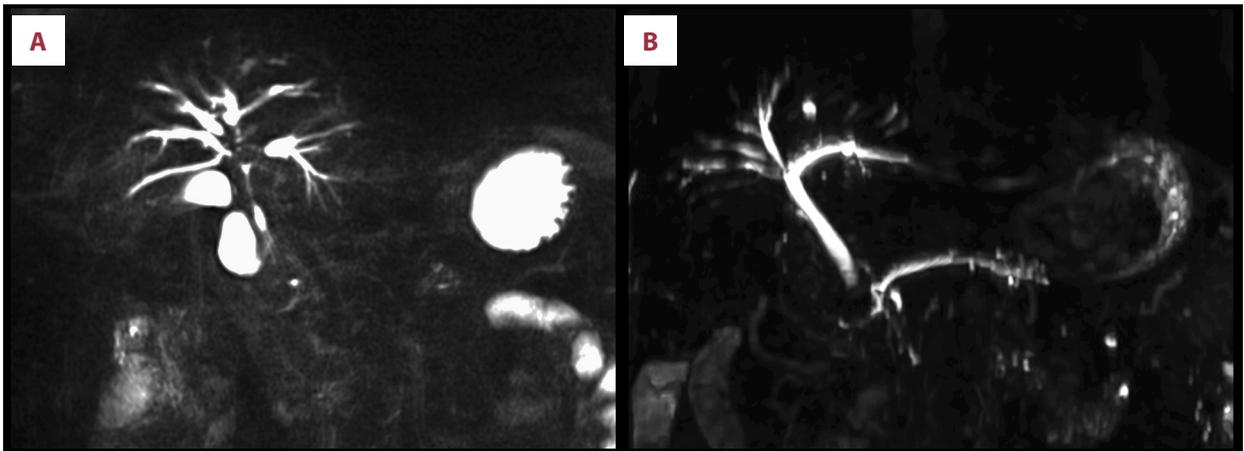
**Figure 2.** **Magnetic resonance cholangiography (MRC) imaging findings.** (**A**) MRC imaging during monotherapy with prednisolone (5 mg/d p. o.) demonstrating relapsed IgG4-SC. MRC findings indicate an occluded common bile duct. Next to this, intrahepatic bile ducts were dilated. (**B**) MRC during treatment with budesonide (9 mg/d p. o.) and low-dose 6-mercaptopurine (50 mg/d p. o.) demonstrating normal intra- and extrahepatic bile ducts without signs of IgG4-SC about 1 year after emergency cholecystectomy.

In the following months, prednisolone was gradually tapered and finally stopped (**Figure 1**), so that maintenance treatment comprised budesonide and low-dose 6-MP (50 mg p. o.). During this treatment, our patient remained in clinical, biochemical, and radiological remission until the end of follow-up (the next 26 months).

Compared to monotherapy with systemic prednisolone (5 mg/d p. o), which resulted in relapsed IgG4-SC (**Figure 2A**) after treatment initiation, there was no recurrence of IgG4-SC during the intake of budesonide and low-dose 6-MP (**Figure 2B**).

During treatment with budesonide (9 mg/d) and 6-MP (50 mg/d), an ACTH test with 0.25 mg Synacthen (tetracosactide) showed an adequate increase of cortisol from 90 µg/L to 173 µg/L 30 minutes after and to 196.4 µg/L 60 minutes after stimulation with tetracosactide. Therefore, secondary adrenal insufficiency was ruled out during treatment with budesonide.

Subsequently, budesonide was tapered from 9 mg to 6 mg and finally to 3 mg, without complications. Furthermore, 6-MP was reduced from 50 mg/d to 30 mg/d. During this treatment, all laboratory values (AST, ALT, γGT, AP, bilirubin, albumin, INR) remained in their normal ranges (**Figure 1**) and abdominal ultrasound showed normal intra- and extrahepatic bile ducts (data not shown). Furthermore, our patient was fully vaccinated against SARS-CoV-2 and received a booster without complications.

## Discussion

Treatment of IgG4-RD is immunosuppressive and glucocorticoids represent a cornerstone of therapy [7]. According to HISORT criteria (Histology, Imaging, Serology, Other organ involvements, and Response to steroid treatment), a response to steroids is also an important diagnostic criterion in IgG4-RD [17,18].

Use of steroids has advantages, but they are unfortunately associated with various adverse effects, including thrombosis, diabetes mellitus, osteoporosis, psychosis, bacterial infection, and secondary adrenal insufficiency [11]. Since IgG4-RD occurs more frequently in elderly patients, with a mean age at diagnosis of about 60 years [19], steroid-related adverse effects may cause serious concern in this patient population and can increase morbidity and mortality [4]. Furthermore, there is evidence that glucocorticoid monotherapy can fail to control IgG4-RD in the long term [5].

In a prospective study, disease relapses occurred in 39% of patients during maintenance treatment with prednisolone (5-10 mg/d) within 1 year after treatment initiation [20]. Furthermore, relapse rates or failure of complete remission of about 40% within the first year despite maintenance administration of prednisolone with a minimum dosage of 5 mg/d have been reported [21].

Patients with multi-organ involvement, high serum IgG4-levels, involvement of the proximal bile duct, and a history of disease relapse are at increased risk for early recurrence of IgG4-RD after remission induction and will most likely benefit from maintenance treatment [5].

Our patient was 70 years old, had involvements of IgG4-RD in multiple organs (IgG4-related-sialadenitis, autoimmune pancreatitis, lymphadenopathy, sclerosing cholangitis), increased serum IgG4-levels (>3.300 g/L), experienced a relapse of IgG4-SC

with involvement of the proximal bile duct (type 4 IgG4-SC) during tapering of prednisolone, and had adverse effects of glucocorticoid treatment, including diabetes and hyperlipidemia [15]. Therefore, a steroid-sparing maintenance treatment seemed reasonable for our patient.

There are conflicting results on the medication and the duration of maintenance treatment after achieving remission in IgG4-RD, and it remains unclear if all patients with IgG4-RD require maintenance treatment [9]. While watchful waiting can be a therapeutic alternative in a minority of patients with asymptomatic single-organ involvement such as dacryoadenitis, sialadenitis, asymptomatic lymphadenopathy, or mild submandibular gland enlargement, patients with symptomatic or organ-threatening disease should be treated with immunosuppressants to reduce morbidity and mortality [9].

Japanese colleagues tend toward a longer steroid course over 3 years with a maintenance dosage of prednisolone of 5-10 mg per day [9]. Western countries (Europe and North America) recommend a shorter steroid treatment and an earlier induction of steroid-sparing agents, such as azathioprine, 6-MP, mycophenolate mofetil, cyclophosphamide, or rituximab [5].

According to the recommendations of the latest European Guideline from 2020 "Immunosuppressive agents should be considered in case of disease relapse as a maintenance of remission strategy, and in patients with a high risk of disease relapse, particularly in the case of multi-organ involvement" [7].

A meta-analysis of 15 studies, which comprised 1169 patients with IgG4-RD, demonstrated that patients who received a combination of steroids and immunomodulators experienced higher remission-free and longer relapse-free rates compared to those treated with steroids alone [8]. Other studies highlighted the use of steroid-sparing agents such as azathioprine in refractory or complicated cases in combination with glucocorticoids [22]. Furthermore, a combined treatment of glucocorticoids along with immunosuppressants such as azathioprine, cyclophosphamide, and mycophenolate mofetil was protective against refractory and relapsed IgG4-RD in a prospective trial [23]. In our patient, immunosuppressive treatment was therefore performed according to the latest recommendations and guidelines [5,7,22,23].

Thiopurines are purine antimetabolites that inhibit DNA and RNA synthesis and lead to apoptosis of T cells [24-27]. In addition to their cytostatic properties, which occur when they are given in higher oncologic doses, they have also immunosuppressive characteristics when given in lower doses [27]. Therefore, thiopurines are used in organ transplant recipients, inflammatory bowel diseases [27,28], and autoimmune hepatitis [29].

Thiopurines lead to a significant depletion of B cells and natural killer cells [30], and apoptosis of activated T lymphocytes [27]. The latter seems to be the main mechanism of action and is related to the metabolite 6-thioguanine nucleotide (6-TGN), which binds to the small GTPase Rac1, thereby inducing apoptosis of activated T lymphocytes [27]. Based on these results, it can be assumed that the immunosuppressive properties of thiopurines are due to their influence on both B and T lymphocytes.

An antigen-driven pathological B and T cell interaction seems to play a causative role in IgG4-RD [9]. Invasion of cytotoxic T lymphocytes in tissue, which lead to the secretion of TGF, IFNγ and IL-1β, and therefore to tissue fibrosis and organ failure, is crucial in the development of IgG4-RD [31,32].

B cell depletion is also an important drug target in IgG4-RD. Specific B cell depletion with, for example, rituximab showed significant improvement of IgG4 disease [9]. However, in addition to the beneficial effects of this treatment in IgG4-RD, the use of rituximab may be accompanied by severe adverse effects [9,33] such as severe transfusion reactions, cytokine release syndrome, neutropenia, cardiac arrhythmias, hypogammaglobulinemia, and bacterial and viral infections, which can cause progressive multifocal leukoencephalopathy due to JC virus, or reactivation of hepatitis B [34]. In addition, a large study demonstrated that treatment with rituximab in the presence of SARS-CoV-2 infection was associated with increased in-hospital mortality. This was not shown for other immunosuppressants such as glucocorticoids, azathioprine, calcineurin inhibitors, mycophenolic acid, interleukin-inhibitors, Janus kinase inhibitors, tumor necrosis factor alpha inhibitors, or cyclophosphamide [35]. Furthermore, a multicenter follow-up study showed that patients treated with rituximab also experienced disease relapses with a rate of up to 40% [33], which indicates the limitation of rituximab as a definitive treatment option for IgG4-RD.

The use of thiopurines, on the other hand, is cost-effective and relatively safe [27]. During the combined treatment with steroids and 6-MP, our patient remained in radiological, biochemical, and clinical remission for his IgG4-RD until the end of follow-up.

However, during treatment with 6-MP, an elevation of transaminases (AST, ALT) occurred only at the time when the dosage was increased from 50 mg to 75 mg/d. Despite normal drug dosing for 6-MP and measurements of 6-MMP-metabolites, which were in the therapeutic range, 6-MP was paused and prednisolone was continued with an increased dosage of 30 mg/d for the next 10 days. These data demonstrate that 6-MP can be hepatotoxic. Since liver values normalized after cessation of 6-MP, the hepatotoxicity was most likely related to a dose-dependent effect of 6-MP.

Elevations of transaminases are the most common hepatotoxic adverse effects in the treatment of 6-MP [36] and dosage reduction or cessation of the drug usually reverses transaminases [37]. Other adverse effects of treatment with 6-MP include myelosuppression, nodular regenerative hyperplasia in the liver, lymphoma, or skin cancers [24]. However, most described adverse effects seem to be rare when thiopurines are administered in lower dosages [27].

At the time when 6-MP was paused due to hepatotoxicity [16], prednisolone was increased (30 mg/d p. o.) for 10 days to prevent a flare of IgG4-SC. In the following course, prednisolone was quickly tapered to 15 mg/d p. o. and budesonide (3 mg/d p. o.) was added to the medication for targeted immunosuppression in the liver to control IgG4-SC.

Budesonide is a synthetic steroid with potent immunosuppressive effects in the liver [38-40]. After oral administration, it undergoes high first-pass metabolism in the liver (90%). Therefore, it causes fewer systemic steroid-related adverse effects compared to treatment with prednisolone [39]. The potent hepatic immunosuppression of budesonide may be due to its high binding affinity to the glucocorticoid receptor and its increased steroid-related effects, which are 240 times higher compared to cortisol and about 60 times higher compared to prednisolone [41]. Its low systemic adverse effects may be explained by the rapid hepatic metabolization [42], whereby its pharmacological metabolites have a 120-fold lower relative binding affinity to the glucocorticoid receptor compared to budesonide [43].

A pilot study demonstrated that budesonide was a safe and effective therapeutic alternative to prednisolone in patients after liver transplantation when it was used in combination with tacrolimus and mycophenolic acid [39]. Further, a randomized trial showed that a combination of budesonide with azathioprine was superior to the combination of azathioprine with prednisolone to induce and maintain remission in patients with autoimmune hepatitis, and patients treated with budesonide experienced fewer steroid-related adverse effects compared to those treated with prednisolone [38]. Furthermore, the efficiency of budesonide as a monotherapy to induce biochemical remission in previously untreated patients with autoimmune hepatitis has been reported [44]. These studies demonstrate that budesonide can provide potent immunosuppression in the liver when it was used alone or in combination with other immunosuppressants. Additionally, budesonide causes fewer systemic adverse effects than treatment with prednisolone [38,39].

It can be assumed that the high local hepatic effect of budesonide ensured adequate immunosuppression in the liver, thereby achieving control of IgG4-SC. Moreover, systemic immunosuppression was provided by 6-MP after the discontinuation of prednisolone. In addition, it can be assumed that 6-MP in combination with locally acting budesonide also had an immunosuppressive effect on IgG4-SC.

Unfortunately, our patient developed gangrenous cholecystitis, which occurred during triple immunosuppressive treatment with prednisolone (10 mg/d p. o.), budesonide (9 mg/d p. o.), and 6-MP (50 mg/d p. o.). This complication was diagnosed within 24 hours. Gangrenous cholecystitis has a higher mortality rate than uncomplicated cholecystitis [45]. Risk factors are increased leucocytes (>15 tsd/μL), diabetes mellitus, age >50 years, late admission to the hospital, and increased CRP values [46-48]. Our patient was 70 years old, and had cholecystolithiasis (1 concretion) and diabetes mellitus after being started on prednisolone 5 years ago, which may have favored the development of gangrenous cholecystitis. Further, he had elevated leukocytes and CRP, which are risk factors for the development of gangrenous cholecystitis.

Overall, the development of gangrenous cholecystitis highlights the complications that can arise during systemic immunosuppressive treatment for IgG4-RD. A known feature in immunosuppressed patients is acalculous cholecystitis, which is acute inflammation of the gallbladder wall in the absence of gallstones [49] and gangrene of the gallbladder occurs in about 60% of patients with acute acalculous cholecystitis [50]. These data give rise to the assumption that immunosuppression may have favored the development of gangrenous cholecystitis in our patient. A causative role of IgG4-RD in the development of gangrenous cholecystitis was very unlikely due to the presence of neutrophil granulocytes and absence of plasma cells in the histological analyzation of the gallbladder.

In the management of acute inflammation for gangrenous cholecystitis, budesonide and 6-MP were paused and prednisolone was continued at 10 mg/d p. o. This was done to lower the risk of a septic course and to ensure immunosuppression for IgG4-RD. Subsequently, when our patient was free of symptoms and laboratory signs of infection resolved, budesonide was administered again at 3 mg/d p. o. and quickly increased to 9 mg/d p. o. in combination with 6-MP (50 mg/d p. o.). Under this treatment, prednisolone was further reduced and finally stopped. Thus, systemic steroid-related adverse effects and steroid-related morbidity were reduced. This is underscored by a negative ACTH test, which ruled out secondary adrenal insufficiency. Subsequently, budesonide was tapered to 6 mg/d p. o. and finally to 3 mg/d p. o., without complications.

During treatment with 6-MP, our patient had persistent megaloblastic erythrocyte volumes (MCV) despite normal values for folic acid, vitamin B12, and activated vitamin B12 (holo-transcobalamin). An increase in MCV during treatment with thiopurines is described as a surrogate marker for adequate 6-TGN

concentrations and regular thiopurine intake [29,51]. These data suggest that our patient was compliant with the intake of 6-MP.

It should be emphasized that prednisolone is the standard care of treatment for remission induction in IgG4-RD. Treatment with budesonide and 6-mercaptopurine was effective when prednisolone was initially used and maintained with a dosage of 10 mg/d. During this treatment, slow tapering of prednisolone was possible so that maintenance therapy with budesonide and 6-mercaptopurine sustained long-term remission of IgG4-SC.

## Conclusions

Budesonide in combination with low-dose 6-MP maintained biochemical, radiological, and clinical remission in our patient with histologically confirmed systemic IgG4-RD and IgG4-SC, who was at high risk for further disease relapses. Systemic manifestations of IgG4-RD may be controlled in the absence of prednisolone by a low dosage of 6-MP. Further studies should investigate the efficiency of budesonide as monotherapy in patients with IgG4-SC but without signs of systemic IgG4-RD.

Gangrenous cholecystitis may occur as a complication of systemic immunosuppression.

### Department and Institution Where Work Was Done

Department of Gastroenterology, Gastrointestinal Oncology, and Endocrinology, University Medical Center Goettingen, Goettingen, Germany.

### Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

## References:

1. Okazaki K, Umehara H. Are classification criteria for IgG4-RD now possible? The concept of IgG4-related disease and proposal of comprehensive diagnostic criteria in Japan. Int J Rheumatol. 2012;2012:357071

2. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366(6):539-51

3. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet. 2015;385(9976):1460-71

4. Akiyama M, Takeuchi T. IgG4-related disease: beyond glucocorticoids. Drugs Aging. 2018;35(4):275-87

5. Khosroshahi A, Wallace ZS, Crowe JL, et al. International Consensus Guidance Statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol. 2015;67(7):1688-99

6. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25(9):1181-92

7. Löhr JM, Beuers U, Vujasinovic M, et al. European guideline on IgG4-related digestive disease – UEG and SGF evidence-based recommendations. United European Gastroenterol J. 2020;8(6):637-66

8. Omar D, Chen Y, Cong Y, Dong L. Glucocorticoids and steroid sparing medications monotherapies or in combination for IgG4-RD: A systematic review and network meta-analysis. Rheumatology (Oxford). 2020;59(4):718-26

9. Zhang W, Stone JH. Management of IgG4-related disease. Lancet Rheumatology. 2019;1(1):e55-65

10. Katz G, Stone JH. Clinical perspectives on IgG4-related disease and its classification. Annu Rev Med. 2022;73:545-62

11. Saag K, Furst D. Major side effects of systemic glucocorticoids – UpToDate [Internet]. 2020 [cited 2021 Mar 1]. Available from: https://www.uptodate.com/contents/major-side-effects-of-system-ic-glucocorticoids?search=major%20side%20effects%20of%20system-ic%20glucocorticoids&source=search_result&selectedTitle=1~150&usag e_type=default&display_rank=1

12. Yunyun F, Yu P, Panpan Z, et al. Efficacy and safety of low dose Mycophenolate mofetil treatment for immunoglobulin G4-related disease: A randomized clinical trial. Rheumatology (Oxford). 2019;58(1):52-60

13. Wallwork R, Harkness T, Fu X, et al. Early mortality in IgG4-related disease. ACR Meeting Abstracts. Available from: https://acrabstracts.org/abstract/early-mortality-in-igg4-related-disease/

14. Kamisawa T, Nakazawa T, Tazuma S, et al. Clinical practice guidelines for IgG4-related sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2019;26(1):9-42

15. Gummlich BP, Ströbel P, Seif Amir Hosseini A, et al. Systemic IgG4-related disease masquerading as cholangiocarcinoma: A case report underscoring the importance of medical history. Am J Case Rep. 2021;22:e930729

16. Fachinformation 6-Mercaptopurin (Puri-Nethol) [Internet]. Available from: https://www.fachinfo.de/api/fachinfo/pdf/002606

17. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: The Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4(8):1010-16

18. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: Guidelines of the International Association of Pancreatology. Pancreas. 2011;40(3):352-58

19. Brito-Zerón P, Ramos-Casals M, et al. The clinical spectrum of IgG4-related disease. Autoimmun Rev. 2014;13(12):1203-10

20. Yunyun F, Yu C, Panpan Z, et al. Efficacy of cyclophosphamide treatment for immunoglobulin G4-related disease with addition of glucocorticoids. Sci Rep. 2017;7(1):6195

21. Perugino CA, Stone JH. IgG4-related disease: An update on pathophysiology and implications for clinical care. Nat Rev Rheumatol. 2020;16(12):702-14

22. Brito-Zerón P, Kostov B, Bosch X, et al. Therapeutic approach to IgG4-related disease: A systematic review. Medicine (Baltimore). 2016;95(26):e4002

23. Zongfei J, Lingying M, Lijuan Z, et al. Prognostic factors in IgG4-related disease: A long-term monocentric Chinese cohort study. Clin Rheumatol. 2021;40(6):2293-300

24. de Boer NKH, van Bodegraven AA, Jharap B, et al. Drug insight: Pharmacology and toxicity of thiopurine therapy in patients with IBD. Nat Clin Pract Gastroenterol Hepatol. 2007;4(12):686-94

25. Tiede I, Fritz G, Strand S, et al. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. J Clin Invest. 2003;111(8):1133-45

26. Quéméneur L, Gerland LM, Flacher M, et al. Differential control of cell cycle, proliferation, and survival of primary T lymphocytes by purine and pyrimidine nucleotides. J Immunol. 2003;170(10):4986-95

27. Boer NKH de, Ahuja V, Almer S, et al. Thiopurine therapy in inflammatory bowel diseases: Making new friends should not mean losing old ones. Gastroenterology. 2019;156(1):11-14

28. Elion GB. Historical background of 6-mercaptopurine. Toxicol Ind Health. 1986;2(2):1-9

29. Lohse AW, Sebode M, Jørgensen MH, et al. Second-line and third-line therapy for autoimmune hepatitis: A position statement from the European Reference Network on Hepatological Diseases and the International Autoimmune Hepatitis Group. J Hepatol. 2020;73(6):1496-506

30. Lord JD, Shows DM. Thiopurine use associated with reduced B and natural killer cells in inflammatory bowel disease. World J Gastroenterol. 2017;23(18):3240-51

31. Mattoo H, Mahajan VS, Maehara T, et al. Clonal expansion of CD4(+) cytotoxic T lymphocytes in patients with IgG4-related disease. J Allergy Clin Immunol. 2016;138(3):825-38

32. Mattoo H, Stone JH, Pillai S. Clonally expanded cytotoxic CD4+ T cells and the pathogenesis of IgG4-related disease. Autoimmunity. 2017;50(1):19-24

33. Ebbo M, Grados A, Samson M, et al. Long-term efficacy and safety of rituximab in IgG4-related disease: Data from a French nationwide study of thirty-three patients. PLoS One. 2017;12(9):e0183844

34. Fachinformation Rituximab (MabThera® i.v.). [Internet]. [cited 2021 Nov 23]. Available from: https://www.fachinfo.de/api/fachinfo/pdf/002730

35. Andersen KM, Bates BA, Rashidi ES, et al. Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: A retrospective cohort study using data from the National COVID Cohort Collaborative. Lancet Rheumatol. 2022;4(1):e33-41

36. Björnsson ES, Gu J, Kleiner DE, et al. Azathioprine and 6-mercaptopurine-induced liver injury: Clinical features and outcomes. J Clin Gastroenterol. 2017;51(1):63-69

37. Shaye OA, Yadegari M, Abreu MT, et al. Hepatotoxicity of 6-mercaptopurine (6-MP) and Azathioprine (AZA) in adult IBD patients. Am J Gastroenterol. 2007;102(11):2488-94

38. Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology. 2010;139(4):1198-206

39. Bari K, Shah SA, Kaiser TE, et al. Safety and efficacy of budesonide for liver transplant immune suppression: results of a pilot phase 2a trial. Liver Transpl. 2020;26(11):1430-40

40. Bhat M, Ghali P, Wong P, et al. Immunosuppression with budesonide for liver transplant recipients with severe infections. Liver Transplantation. 2012;18(2):262-63

41. Scholz T. Agonismus synthetischer Glukokortikoide am Gluko- und am Mineralokortikoidrezeptor des Menschen in einem CV-1-Zellsystem [Internet]. Charité – Universitätsmedizin Berlin Campus Benjamin Franklin; 2004 p. 66-67. [cited 2021 Jun 20]. Available from: https://refubium.fu-berlin.de/handle/fub188/5517 [in German]

42. Dahlberg E, Thalén A, Brattsand R, et al. Correlation between chemical structure, receptor binding, and biological activity of some novel, highly active, 16 alpha, 17 alpha-acetal-substituted glucocorticoids. Mol Pharmacol. 1984;25(1):70-78

43. Rohdewald P, Rehder S, Würthwein G. Rezeptoraffnität synthetischer Glukokortikoide. In: Schulte HM (Hrsg), Therapie mit Glukokortikoiden: Molekularbiologische, pharmakologische und klinische Aspekte/2. Nebennierenkonferenz 1991, Schattauer 1993;39-50 [in German]

44. Wiegand J, Schüler A, Kanzler S, et al. Budesonide in previously untreated autoimmune hepatitis. Liver Int. 2005;25(5):927-34

45. Önder A, Kapan M, Ülger BV, et al. Gangrenous cholecystitis: Mortality and risk factors. Int Surg. 2015;100(2):254-60

46. Fagan SP, Awad SS, Rahwan K, et al. Prognostic factors for the development of gangrenous cholecystitis. Am J Surg. 2003;186(5):481-85

47. Chaudhry S, Hussain R, Rajasundaram R, Corless D. Gangrenous cholecystitis in an asymptomatic patient found during an elective laparoscopic cholecystectomy: A case report. J Med Case Rep. 2011;5(1):199

48. Merriam LT, Kanaan SA, Dawes LG, et al. Gangrenous cholecystitis: Analysis of risk factors and experience with laparoscopic cholecystectomy. Surgery. 1999;126(4):680-85; discussion 685-86

49. George J, Cohen M, Whitney S, et al. Biliary disease in immunocompromised patients: A single-center retrospective analysis. J Gastrointest Surg. 2019;23(8):1589-92

50. Kalliafas S, Ziegler DW, Flancbaum L, Choban PS. Acute acalculous cholecystitis: Incidence, risk factors, diagnosis, and outcome. Am Surg. 1998;64(5):471-75

51. Bouguen G, Sninsky C, Tang KL, et al. Change in erythrocyte mean corpuscular volume during combination therapy with azathioprine and infliximab is associated with mucosal healing: A post hoc analysis from SONIC. Inflamm Bowel Dis. 2015;21(3):606-14