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**EDITORIAL**

O'Neill RS, Nandakumaran J, Feller R. Sirolimus and gastrointestinal angiodysplasia: Can an established agent change the way gastrointestinal bleeding is managed? *World J Gastroenterol* 2025; 31(41): 113736 [DOI: [10.3748/wjg.v31.i41.113736](https://doi.org/10.3748/wjg.v31.i41.113736)]

**REVIEW**

Han JF, Jia ZY, Fan X, Zhao XY, Cheng LY, Xia YX, Ji XR, Zang WQ. Mechanisms of ferroptosis in primary hepatocellular carcinoma and progress of artificial intelligence-based predictive modeling in hepatocellular carcinoma. *World J Gastroenterol* 2025; 31(41): 111174 [DOI: [10.3748/wjg.v31.i41.111174](https://doi.org/10.3748/wjg.v31.i41.111174)]

**ORIGINAL ARTICLE****Retrospective Cohort Study**

Xiang Y, Yang N, Zheng TL, Huang YF, Liu TY, Ma DQ, Hu SJ, Zhang WH, Xiang HL, Zhang LY, Yuan LL, Wang X, Dang T, Zhang G, Wu B, Peng LJ, Gao M, Xia DL, Liu ZB, Li J, Song Y, Zhou XQ, Qi XS, Zeng J, Tan XY, Deng MM, Fang HM, Qi SL, He S, He YF, Ye B, Wu W, Shao JB, Wei W, Hu JP, Yong X, He CH, Bao JL, Zhang YN, Ji R, Bo Y, Yan W, Li HJ, Li SL, Geng S, Zhao L, Liu B, Qi XL. Development of a deep learning model for guiding treatment decisions of acute variceal bleeding in patients with cirrhosis. *World J Gastroenterol* 2025; 31(41): 111361 [DOI: [10.3748/wjg.v31.i41.111361](https://doi.org/10.3748/wjg.v31.i41.111361)]

**Retrospective Study**

Wu JW, Li LP, Chen YS. Effects of bottle gourd moxibustion combined with umbilical therapy for cancer-related incomplete bowel obstruction on inflammatory cytokine levels. *World J Gastroenterol* 2025; 31(41): 110753 [DOI: [10.3748/wjg.v31.i41.110753](https://doi.org/10.3748/wjg.v31.i41.110753)]

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**Observational Study**

Weng MT, Yao CY, Lin WC, Lai SK, Tung CC, Wang CY, Wong JM, Chen PL, Wei SC. HLA-C\*03:04:01 and HLA-B\*15:18:01 but not HLA-DQA1\*05 associated with anti-tumor necrosis factor antibody formation in Taiwanese inflammatory bowel disease patients. *World J Gastroenterol* 2025; 31(41): 111745 [DOI: [10.3748/wjg.v31.i41.111745](https://doi.org/10.3748/wjg.v31.i41.111745)]

**Basic Study**

Ruiz-Malagón AJ, Herraiz-Vilela M, Serrano-Pino R, García-Ávila P, Díaz-Suárez L, Carmona-Segovia AD, Becerra-Munoz VM, Jiménez-Navarro M, Arranz-Salas I, López-Villodres JA, Fernández-Castañer A, Gutiérrez-Martínez F, Rodríguez-González FJ, Camargo-Camero R, Alcáin-Martínez G, Rodríguez-Díaz C, García-Fuentes E, Sánchez-Quintero MJ, López-Gómez C. Growth differentiation factor 15 alters intestinal barrier and increases permeability: A new molecular target in inflammatory bowel disease. *World J Gastroenterol* 2025; 31(41): 110955 [DOI: [10.3748/wjg.v31.i41.110955](https://doi.org/10.3748/wjg.v31.i41.110955)]

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**CASE REPORT**

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## Sirolimus and gastrointestinal angiodysplasia: Can an established agent change the way gastrointestinal bleeding is managed?

Robert Sean O'Neill, Jeyvin Nandakumaran, Robert Feller

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### Abstract

Gastrointestinal angiodysplasia (GIAD) is a common, acquired, vascular abnormality in the gastrointestinal tract that is commonly implicated in bleeding. Sirolimus, also known as rapamycin, is a mammalian target of rapamycin pathway inhibitor that has shown significant potential in inhibiting abnormal angiogenesis that has demonstrated efficacy in inhibiting abnormal blood vessel formation in the skin, cornea, and tumors. Sun *et al* in their single centre prospective study aimed to evaluate the efficacy and safety of sirolimus in treating GIAD-associated bleeding. While their study does provide a sound platform for future studies to investigate the effects of sirolimus in the treatment of GIAD-associated bleeding in an evidence free zone, there are limitations to the study which are not addressed. In this commentary, we summarise the significant highlights from the study performed by Sun *et al* along with its limitations. In addition to this, we provide an update on the current therapies utilised in the treatment of GIAD-associated bleeding.

**Key Words:** Gastroenterology; Angiodysplasia; Gastrointestinal bleeding; Sirolimus; Bleeding

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**Core Tip:** This article discussed the current treatment landscape of gastrointestinal angiodysplasia (GIAD) with a focus on pharmacological management rather than endoscopic management. It also examines the study by Sun *et al.*, who demonstrated in their small single-centre study that sirolimus, a mammalian target of rapamycin inhibitor, reduced bleeding and transfusion needs while improving haemoglobin levels in GIAD patients.

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## INTRODUCTION

Gastrointestinal angiodysplasia (GIAD) is a common, acquired, vascular abnormality of the gastrointestinal tract that is commonly implicated in bleeding. They are usually multiple in number and found throughout the gastrointestinal tract, however they have a predominance for the proximal jejunum and ascending colon[1]. With reference to their pathophysiology, chronic tissue ischaemia leads to the increased secretion of vascular endothelial growth factors (VEGF) with subsequent upregulation of angiogenesis, resulting in the formation of these vascular abnormalities that are a common source of occult gastrointestinal bleeding in patients with critical aortic stenosis, chronic obstructive pulmonary disease, hypertension, ischaemic heart disease, chronic kidney disease, heart failure and chronic liver disease[2].

Diagnosis and treatment of GIAD relies on oesophagogastroduodenoscopy and colonoscopy, while small bowel GIAD diagnosis usually requires capsule endoscopy with subsequent device-assisted enteroscopy required for treatment[3,4]. With regards to the treatment of GIAD, endoscopic therapy utilizing thermocoagulation is recognised as the mainstay of therapy however there is a significant risk of rebleed, with rates ranging from 35%-80% post endoscopic treatment[5,6]. In addition to this, mechanical clip placement and multipolar electrocoagulation have also been demonstrated to possess efficacy in the treatment of GIAD[7].

We read with interest the recent article published by Sun *et al*[8] in *World Journal of Gastroenterology*, who reported on a self-controlled prospective study that also encompassed retrospective data pertaining to a small group of patients treated with oral sirolimus over a period ranging from three to fifteen months. Based on the limited study size, the authors were able to demonstrate a significant reduction in bleeding episodes in the follow up period compared to the 3-month pre-treatment period, as well as improving haemoglobin levels and reducing transfusion volume and frequency compared to the pre-treatment period, with only two patients in the cohort requiring blood transfusions during the treatment period. This was however confounded by significant comorbidities and high lesion load diagnosed on index assessment. The authors also reported that sirolimus reduced vascular lesions with improvement in lesion size and characteristics, however this was not objectively measured across their study. Although a relatively high adverse reaction rate was reported by the authors in patients receiving sirolimus, only a single patient was required to cease sirolimus due to pulmonary infection, therefore highlighting an acceptable safety profile based on the limited cohort size.

Sirolimus inhibits the mammalian target of rapamycin (mTOR) signalling pathway, suppressing tumor angiogenesis and limiting tumor growth and metastasis. The drug is more commonly utilized as an immunosuppressant in the context of solid organ transplantation[9,10]. With reference to GIAD, sirolimus is a relatively novel agent with studies limited to case reports assessing its role in the context of colonic angioectasia with demonstrated efficacy in reducing clinical bleeding along with transfusion requirements over a 6-month period[8]. With reference to its action from a vascular perspective, as an mTOR inhibitor, it regulates angiogenesis and inflammation, resulting in sustained bleeding control with a modest side effect profile.

The study by Sun *et al*[8] does provide preliminary evidence in an evidence free zone, however methodologically there are limitations. Although all patients were screened with either video capsule endoscopy (VCE) or double balloon enteroscopy (DBE), monitoring for GIAD related bleeding was *via* biweekly fecal occult blood test (FOBT). Fecal occult blood testing has limited sensitivity and specificity in the diagnosis of GIAD related bleeding, thus potentially limiting the conclusion of the study that sirolimus reduced bleeding related to GIAD. Further to this, in their follow up, it is not mentioned which patients underwent VCE or DBE to evaluate GIAD in the post-treatment period. It has been previously demonstrated that device assisted endoscopy, which includes DBE, is superior to VCE with regards to diagnostic and therapeutic yield[11]. This modality has both diagnostic and therapeutic value, however, it is more invasive and has the potential for complications. In the post treatment period, no patient underwent endoscopic or surgical intervention, therefore the utility of DBE for surveillance in the post-treatment period is questionable given the study findings and thus poses an unnecessary risk. Future studies should aim to explore the use of VCE in monitoring of GIAD related bleeding treated with sirolimus with a view to identify which patients require further intervention (DBE or surgical) and the subsequent rate of intervention. If indeed the findings of Sun *et al*[8] are generalizable, and the rate of endoscopic intervention is dramatically impacted by sirolimus in GIAD, then this proves to be an extremely promising tool in the treatment of GIAD, given the significant burden recurrent endoscopic procedures places on patients and the economic burden placed on their respective healthcare systems. In addition to this, the inclusion criteria for the study included patients who had at least four episodes of bleeding, however this was not defined in the study, namely whether it was overt gastrointestinal bleeding or bleeding detected by FOBT analysis. Further to this, the outcome of gastrointestinal

bleeding post intervention is not clearly defined in the study highlighting a limitation of the study methodology.

A common patient factor identified in patients with GIAD is that of chronic kidney disease, as well as chronic liver disease or critical aortic valve disease. It should be noted that in the presented study by Sun *et al*[8], patients with 'serious health' conditions, such as chronic kidney disease, cirrhosis or severe cardiovascular disease were excluded from participating in the trial. This indeed limits the generalisability of the findings in the study and does somewhat reduce the quality of the results. Given the tendency for patients with these significant comorbidities to represent a large proportion of patients who present with GIAD related bleeding requiring intervention, further studies should aim to incorporate them into study analysis thus potentially opening up the use of sirolimus to a wider patient cohort. Aside from determining whether sirolimus is effective in these patient subgroups, it would also be pertinent that a safety analysis is performed prior to consideration of its use in clinical practice. In addition to this, a further limitation of this study with regards to the cohort selection is that the study was performed in a Chinese population only. This does limit the generalizability of the study findings to other populations, however, it does highlight an area for future research.

Sirolimus dosing in the presented study was based on evidence pertaining to treatment for lymphangiioleiomyomatosis and blue rubber bleb nevus syndrome[12,13]. The study itself did not report on sirolimus trough levels and their correlation with clinical outcomes despite reporting that plasma concentrations being taken a 1-, 3- and 6 months post commencement. Given the small study numbers, it is likely that extrapolating conclusions from trough levels would not be meaningful in terms of determining whether there was a dose related response in clinical outcomes, however further studies should aim to assess this in the case of GIAD. If indeed this is the case, dose optimization of sirolimus in patients with GIAD should be evaluated to determine whether a standardized dosing regimen can be implemented for patients with GIAD rather than extrapolating from separate disease entities.

Current pharmacological therapies for GIAD are limited, with somatostatin analogs (SSA) such as lanreotide, octreotide and pasireotide being investigated over the past two decades in observational studies and randomized controlled trials. SSA work by decreasing splanchnic blood flow to the gastrointestinal tract, increasing platelet aggregation and suppressing angiogenic factors through VEGF downregulation[14,15]. Although significant variation does exist between studies examining the role of somatostatin analogues in the treatment of GIAD, namely in the areas of cohort size, patient cohorts, inclusion criteria and study design, the majority of studies demonstrate an improvement in haemoglobin levels and reduction in bleeding. Although promising with regards to the treatment of GIAD, aside from a single large observational study published by Gutierrez *et al*[16], the vast majority of studies examining the efficacy of somatostatin analogues in GIAD are limited to small sample sizes. The landmark OCEAN Study published by Goltstein *et al*[17] is perhaps the most seminal paper regarding the use of SSAs in GIAD which demonstrated a reduction in blood transfusions and the annual volume of endoscopic procedures in those treated with LAR octreotide 40 mg monthly compared to the standard therapy group (endoscopic argon plasma coagulation)[17]. Although a benefit has been recognised, 20% of patients treated report adverse events, including but not limited to diarrhoea, abdominal pain, and cholelithiasis[18].

Thalidomide is a relatively new addition to the armory in the treatment of GIAD, with the placebo-controlled randomized trial published by Chen *et al*[19] in *The New England Journal of Medicine* providing the catalyst sparking further research into the area of treatment of GIAD. In their multi-center, double-blind, randomized, placebo-controlled trial, they were able to demonstrate an 'effective response' to thalidomide in patients with GIAD, defined as a reduction of at least 50% in the number of bleeding episodes in the year post thalidomide treatment. Similarly to the presented study by Sun *et al*[8], patients with cirrhosis or renal failure were excluded in the treatment group highlighting a similarity in patient cohorts. Further meta-analysis data has reinforced these findings, with Song *et al*[20] reporting on an improved mean change in haemoglobin levels without severe adverse effects in those treated with thalidomide for GIAD. Outside of Asia, the literature pertaining to the use of thalidomide in GIAD is limited to case series and as such this does pose a potential future research direction in the field of GIAD pharmacotherapy[18].

Bevacizumab, a humanized anti-VEGF monoclonal antibody that bind specifically to VEGF thus negating its action on endothelial VEGF receptors, has previously demonstrated efficacy in the treatment of gastric antral vascular ectasia and hereditary haemorrhagic telangiectasia[21-23]. In the case of GIAD, studies are limited to case reports, case series and small retrospective studies, however based on limited studies with small sample sizes and likely publication bias, preliminary data is promising with a reduction in red cell transfusion requirements and the need for endoscopic procedures[21,24,25]. Given the limited evidence along with the risk of thromboembolism, bowel perforation, nephropathy and bleeding, it is difficult to justify the use of bevacizumab outside the realm of the research setting and as such further prospective randomized controlled trials need to be undertaken prior to its routine use in patients with GIAD.

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## CONCLUSION

In summary, the treatment landscape for GIAD is quite limited with a definitive lack of large multi centre prospective trials evaluating the use of both existing and novel agents. GIAD poses a large clinical burden on patients and their respective healthcare providers given the need for recurrent transfusions, endoscopic intervention and in the rare case, surgery. The authors present an important, small single centre self-controlled prospective study encompassing retrospective data that acts as a proof-of-concept study for sirolimus in the treatment of GIAD[8]. Despite its merit in demonstrating favourable clinical outcomes in patients with regards to bleeding events, transfusion requirements and haemoglobin levels, limitations exist with the methodology along with the included patient cohort that limits the generalisability of this study. The exclusion of specific patient subgroups, namely those with chronic kidney disease, chronic

liver disease and critical aortic valve disease affects the applicability of the results of this study to the broader GIAD population and as such requires further research prior to implementation in practice for the treatment of GIAD. As to where sirolimus may fit in the treatment of GIAD in the future, given its preliminary favorable clinical outcomes in treating patients with GIAD, sirolimus may prove to be adjunctive agent in the treatment of GIAD in addition to endoscopy with a multimodal approach proving to be beneficial in patients plagued with recurrent gastrointestinal bleeding. Further research will be essential to determine whether these findings are generalizable with a hope that sirolimus may be the new weapon in the fight against GIAD.

## FOOTNOTES

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