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Kidney function monitoring to prevent 5-aminosalicylic acid nephrotoxicity: what the gastroenterologist should know

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LG wrote the article. LG and LPB conceived the study. FD, HA, CA, FG, SD, LF, LPB critically revised the manuscript. The manuscript was approved by all authors.

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Abstract (209 words)

Background: The kidney function monitoring is recommended in routine practice to detect 5-aminosalicylic acid (5-ASA) related nephrotoxicity, although is not standardized. The optimal monitoring is unknown, especially the best timing and which tests to perform. We summarized why, how, and when to perform the monitoring for patients treated with 5-ASA and provided an overview of the current guidelines on this topic.

Method: Relevant studies on this topic were searched in PubMed, Embase, and Web of Science databases from July to August 2020.

Results: Serum creatinine, the estimated glomerular filtration rate, and 24-hours proteinuria are the 3 main tests used for the monitoring in daily practice. Regarding the timing, several monitoring strategies have been proposed and guidelines are available too, but they provide conflicting information. To date, there is no medical evidence-based that one strategy is better than another. Comorbidities, chronic renal disease, use of nephrotoxic drugs or concomitant steroid therapy also impact the nephrotoxicity risk. Based on the literature review we proposed a kidney function monitoring strategy to guide physicians in clinical practice.

Conclusion: A baseline assessment should be performed in all patients treated with 5-ASA. The monitoring should be carried out according to the other nephrotoxic factors. A tight monitoring may reduce morbidity and mortality of drug nephrotoxicity.

Keywords: Inflammatory bowel diseases, ulcerative colitis, mesalamine, monitoring, kidney insufficiency

Introduction

Mesalamine (or 5-aminosalicylic acid, 5-ASA) is the main drug for the therapeutic management of patients with mild-moderate ulcerative colitis (UC) and in the past decades it was also frequently used in patients with Crohn's disease (CD)^{1,2}. Based on current recommendations, 5-ASA remains the backbone therapy for mild to moderate UC, and is used in more than 50% of patients^{1,3-5}. For moderate to severe UC patients, 5-ASA use may reduce the risk of colon cancer¹. Although its overall safety profile is similar to placebo, some cases of nephrotoxicity have been reported^{6,7}. The pathophysiological mechanisms of induction and the initial site of renal damage are unknown⁸. 5-ASA has structural similarities to both phenacetin-derived analgesics and salicylates, which leads to necrosis of proximal convoluted tubules and renal papilla in rats^{9,10}. Mesalamine first demonstrated nephrotoxicity in preclinical studies in rats and dogs¹¹. However, in vitro studies on 5-ASA-related kidney cell damage could not find an explanation for the occurrence of tubulointerstitial nephritis¹². One pathophysiological explanation may be that salicylates inhibit the synthesis of intra-renal prostaglandins, which are vasoactive mediators of intra-renal blood flow, and decouple oxidative phosphorylation in mitochondria^{13,14}. High intra-renal concentrations of salicylates also inhibit the pentose phosphate shunt reducing renal glutathione and making the kidney susceptible to oxidative damage¹⁵.

The main renal damage presentation is an indolent, severe, chronic, and progressive interstitial nephritis, but nephrotic syndrome and glomerulonephritis are also described^{8,16-19}. 5-ASA nephrotoxicity is a rare drug complication^{20,21}. Renal impairment occurrence is idiosyncratic, without dose or drug relationship, in most cases within the first 12 months, but it can be delayed and occur after several years^{8,16,20,22}. Nephrotoxicity can be a serious complication, and delays in diagnosis and treatment discontinuation can lead to end-stage

renal failure^{8,23–25}. For this reason, kidney function monitoring is currently recommended in daily clinical practice in order to detect this potentially fatal complication^{1,20}. To date, although several recommendations are available, there is no commonly accepted guide for monitoring renal function in patients undergoing mesalamine treatment and the optimal monitoring program remains unknown^{20,26–31}. Here, we reviewed available studies and current recommendations on monitoring of kidney function during 5-ASA treatment. We summarized why, how, and when to perform the monitoring, providing clinicians with a guide for daily clinical practice.

Methods

Two authors (LG and FD) searched in PubMed, Embase, and Web of Science databases from July to August 2020 to identify relevant studies on this topic. The following Medical Subject Heading (MeSH) terms alone or matched with the Boolean operators “AND” or “OR” were used: “mesalamine”, “5-ASA”, “nephrotoxicity”, “kidney diseases”, “inflammatory bowel disease”, “Crohn disease”, “ulcerative colitis”, “renal insufficiency”, “kidney failure”, “drug monitoring”, “guideline”. Two authors (LG and FD) independently screened titles and abstracts. All editorials, notes, comments, or letters were excluded. Articles were selected on the basis of their clinical relevance and full-text manuscripts were analyzed for inclusion. Any disagreements between investigators were resolved through collegial discussion. Finally, we accurately checked the reference lists of the included studies for any additional relevant work.

What is the magnitude of the risk?

Available evidence of the nephrotoxicity

5-ASA nephrotoxicity is a rare condition^{20,21}. Its incidence ranges from 1 case per 4,000 person-years (py)³² to 1.7 per 1,000 py¹⁶ in two British studies. In the first one, 59 news cases of nephrotoxicity were identified by the British Society of Gastroenterology (BSG) during a two-years prospective study³². In the second study, 130 out of 19,025 IBD patients using 5-ASA developed renal disease from the United Kingdom General Practice Research Database¹⁶. In addition, the prevalence of deterioration of kidney function after 5-ASA treatment is of 0.06% according to the safety data from 18 clinical trials assessing the efficacy of 5-ASA in 1,638 IBD patients³³; this prevalence rate is low, but the follow-up was only of 6 to 12 months, thus underestimating it. In 2007, a systematic review by Gisbert et al.²² described 46 cases of 5-ASA-related renal disease (e.g. interstitial nephritis, nephrotic syndrome, or glomerulonephritis) in patients with inflammatory bowel diseases (IBD), suggesting an increased risk due to 5-ASA treatment. Among 2,671 IBD patients receiving 5-ASA therapy who were regularly monitored with serum creatinine or creatinine clearance, the mean overall risk of nephrotoxicity was 0.3% and the mean annual risk was 0.26%²². However, it is difficult to define whether this study population is representative of the incidence of this condition as the denominator of the cohort is unknown and could therefore lead to an underestimation of the problem. On the other hand, in a 4-year follow-up retrospective study including 150 patients, 62 of whom were receiving 5-ASA, no significant difference between the two groups was found in terms of serum creatinine and creatinine clearance, and no drug-related renal impairment event occurred³⁴. This study did not find an association between 5-ASA and renal disease, but given the prevalence of this complication, not enough patients were included to draw definitive conclusions. In a recent retrospective cohort study based on the Health Improvement Network (THIN), a United Kingdom's primary care database, and including 355,601 patients with IBD, no significant association was detected between 5-ASA users and non-users³⁵. Interestingly, nephrotoxicity was rather

associated with disease status (e.g. disease duration or active flare-up), comorbidity (e.g. diabetes or cardiovascular diseases), and use of other nephrotoxic drugs (e.g. thiopurine, methotrexate, ciclosporin, or steroids)³⁵. This study had some limitations and the main message should be carefully considered. Firstly, data came from medical records about prescriptions issued rather than dispensed. Secondly, authors looked for “chronic kidney disease” and not acute kidney disease, thus missing events potentially related to 5-ASA. In fact, most of the time 5-ASA nephrotoxicity is an acute event and resolves upon treatment discontinuation allowing for complete recovery of renal function²². Finally, all confounding factors were not taken into account and a sporadic or weak nephrotoxic effect of 5-ASA could not be excluded³⁵. In a 1-year prospective cohort study including 1,529 patients with IBD, half of them used 5-ASA and no difference could be observed in renal impairment (measured by creatinine clearance) between 5-ASA users and non-users at baseline and after 6 and 12 months²¹. The 1-year follow-up was probably not long enough to detect a significant difference. Moreover, creatinine clearance is no longer used in daily practice to assess kidney function due to the large variability, difficulty, and cost of measurements³⁶.

Impact of kidney function monitoring

Routine kidney function monitoring is a simple and inexpensive strategy and could allow early diagnosis of renal dysfunction preventing the onset of severe forms of nephrotoxicity^{8,32}. In a nationwide survey, most physicians (205/249, 82%) reported they always performed the monitoring, and only 1% declared to never follow it³⁷. Regarding patients' experience, a survey revealed that the monitoring compliance rate was very high (84.7%)³⁸. Based on these data, it is therefore possible to state that the follow-up of kidney function is well accepted by both patients and physicians. Usually, renal impairment resolves after drug withdrawal^{8,18,22,23,39,40}. 5-ASA discontinuation leads to restoration of kidney

function in 40-85% of cases when the diagnosis is made within 10 months of starting therapy^{18,22}. The time to recovery of kidney function after drug withdrawal ranges from a few weeks to one year²². However, when the diagnosis is delayed beyond 18 months from the start of therapy, only one-third of patients achieve a recovery of kidney function and this is usually only partial¹⁸. In addition, some patients develop an end-stage renal failure and they need for dialysis^{8,23-25}. Another study reported a 61% frequency of residual chronic renal insufficiency and up to 13% of developing end-stage renal disease³⁹. In case of partial recovery or persistent renal failure after stopping 5-ASA, a biopsy should be performed^{8,19,23,39}. Steroids or thiopurines may be considered to improve kidney function, but evidence for a beneficial role is anecdotal and other studies did not show significant effects^{8,18,19,23,39,41}. Moreover, other renal manifestations (e.g. nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, or amyloidosis) are also possible along IBD course and it is difficult to distinguish these events from drug-induced nephrotoxicity⁴²⁻⁴⁵. In daily practice, drug withdrawal is the only way to improve renal damage. The regular monitoring allows early diagnosis of renal failure and is therefore a key factor to prevent the 5-ASA related nephrotoxicity.

What is the evidence supporting the optimal monitoring strategy?

To date, there is no evidence in the literature favoring one kidney function monitoring than another and several protocols have been proposed^{22,26}. Therefore, there is a wide variability in the tests performed and in their frequency. Moreover, current recommendations often do not specify the type and/or the frequency of monitoring of kidney function^{20,26-31}. Hence, there are no clear guidelines to perform the correct follow-up in these patients.

Which tests should be used?

Urinary tests could be useful to monitor the kidney function. Proteinuria and 24-hours proteinuria are used in daily practice to detect renal impairment^{7,37,42,46}. However, microalbuminuria is found in the majority of patients with IBD, and it was demonstrated that microalbuminuria and proteinuria are related to disease activity⁴⁶⁻⁵². This finding may reduce the reliability of proteinuria in this setting. Nevertheless, 24-hours proteinuria is still widely used to assess kidney function, in particular for nephrotic syndrome^{53,54}. Additional tubular urinary markers such as β -N-acetyl-D-glucosaminidase (β -NAG) or immunoglobulin G4 (IgG4) clearance could be considered and may be more sensitive and specific because they are not influenced by disease activity^{42,55,56}. However, in IBD no significant association with 5-ASA nephrotoxicity has been demonstrated, and they are not yet available as a screening method^{42,47,57,58}. Serum creatinine is the simplest test and is broadly used for the monitoring^{7,18,21,22,25,32-34,42,46,59,60}. Although its use is established to assess the kidney function, some shortcomings of its reliability are well known (e.g. age, height, nutritional state, ethnicity, sex, intensive sports activity, cirrhosis, or antibiotic use)^{22,61,62}. Finally, the estimated glomerular filtration rate (eGFR) seems to be the most reliable marker of kidney function⁴². The eGFR is related to serum creatinine and is a parameter that also takes into account age, gender, and sometimes ethnicity (e.g. Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI))⁶². The eGFR is a simple test and is mainly used for the monitoring^{32,34,35,42,44,60}. For the calculation of eGFR, MDRD and CKD-EPI equations are more accurate than the Cockcroft-Gault equation⁶². Indeed, the Cockcroft-Gault equation has several limitations as it is not calibrated for the newer assay methods of serum creatinine, includes the weight which underestimates GFR in obese or edematous individuals, and does not assess a variable for race, leading to a GFR underestimation in Afro-American people⁶². Conversely, MDRD and CKD-EPI tools take into account the Afro-American ethnicity and exclude weight in their equation, resulting

in a lower risk of bias⁶². Among the different eGFR calculation methods, MDRD seems to be the most used one^{32,42}. Indeed, MDRD demonstrated to be a strong and reliable way to monitor eGFR and so kidney function, with a high concordance between kidney function estimates and GFR measured through the Food and Drug Administration (FDA)-assigned kidney function categories⁶³.

In a nationwide survey about kidney function monitoring, 99% of respondents used eGFR with MDRD, 51% the creatinine clearance, 41% were monitored through blood electrolytes, 39% through the 24-hours proteinuria, and 22% used dipsticks³⁷. In a study reporting the patients' experience, serum creatinine and eGFR were used in 97.2% of cases, while 24-hours proteinuria was used less frequently (69.4%)³⁸. Serum creatinine and eGFR are the most commonly performed tests to monitor the kidney function, both in the literature and in daily practice. The 24-hours proteinuria is less used, but it can provide additional data for monitoring, especially for nephrotic syndrome for which it is diagnostic criterion.

When to assess the kidney function?

Most of the time, a baseline assessment of the kidney function is done before starting treatment with 5-ASA^{8,25,42}. The monitoring must be performed throughout the treatment with 5-ASA and periodically in order to guarantee an early diagnosis of renal failure²². Several protocols have been proposed and they are all summarized in *Table 1*^{8,25,33,42,44}. Despite the lack of well-defined and medical evidence-based recommendations, it is a common assumption that the assessment of renal function should be performed before starting treatment. Likewise, the monitoring should be closer during the first year of treatment and then it should be performed every six months or annually. In daily practice, most physicians prescribe the kidney function monitoring twice a year, and a baseline assessment is performed by 59% of practitioners³⁷. On the patients' side, a survey reported that the renal monitoring

was performed twice or ≥ 3 times per year by 44.4% and 41.7% of patients, respectively³⁸. In addition, increased monitoring frequency is warranted in patients receiving concomitant steroid therapy as this may mask the development of significant damage^{18,22}. Finally, attention should be paid to patients with chronic renal failure and IBD using 5-ASA, as it is well known that these patients are more likely to be affected by pre-renal uremia and nephrotoxic agents^{22,64}.

Current guidelines and proposed monitoring strategy

Experts' recommendations

Currently, there is no evidence that one kidney function monitoring strategy is better than another to prevent the nephrotoxicity related to 5-ASA^{22,26}. However, due to the potential severity of this complication, national and international expert groups provided some guidance for clinical practice. We summarized details of these experts' recommendations in *Table 2*^{20,26-31,65,66}. All experts agree on the need for a regular evaluation of the kidney function in patients treated with 5-ASA. However, some of these statements are unclear as modalities and frequency of this monitoring are not rigorously specified. Two experts' groups recommend performing a baseline assessment of kidney function monitoring^{30,31}. The European Crohn's and Colitis Organisation (ECCO) also recommends that physicians should pay attention to patients with pre-existing renal impairment, significant co-morbidities, or those taking additional nephrotoxic drugs^{20,26}. Finally, the Food and Drug Administration's mesalamine handbook advises all patients to undergo a renal function assessment prior to initiation and periodically during mesalamine therapy (*Table 2*)^{67,68}. In addition, patients with preexisting renal disease should be carefully monitored especially during the initial phase of treatment, although authors do not specify for how long and how often^{67,68}. The discrepancy between these guidelines reflects the fact that the optimal monitoring program is not yet

established. Moreover, these monitoring schemes rely more on expert discussion rather than on evidence-based data.

Proposal for a monitoring strategy

We have shown that several monitoring schemes are available, but clear guidelines specifying how often and which tests to perform are still lacking. Thus, gastroenterologists can get lost in all this conflicting information. Based on literature review and current recommendations, we propose a kidney function monitoring strategy to guide physicians (*Figure 1*). All patients treated with 5-ASA should have a baseline evaluation of their kidney function. Comorbidities (e.g. hypertension, diabetes), chronic renal disease, use of nephrotoxic drugs, and concomitant steroid therapy should be assessed before starting the treatment. If one of these situations is met, kidney function should be monitored every 3 months. If not, the monitoring should be done every 3 to 4 months for the first year, then every 6 months. Kidney function should be assessed until 5-ASA is stopped. The monitoring should be performed using serum creatinine, eGFR with MDRD equation, and 24-hours proteinuria. In case of ascertained chronic renal disease, it could be also useful to discuss about alternative therapy and to choose the adequate treatment strategy following the nephrologist's advice.

Conclusion

UC patients treated with 5-ASA are at risk of developing a rare and idiosyncratic renal damage, but the nephrotoxicity can go up to end-stage renal disease requiring dialysis. When it is promptly diagnosed, stopping treatment is usually sufficient for the total recovery. The need for a kidney function monitoring is widely admitted by physicians in daily practice to prevent this complication and is also well accepted by patients. Serum creatinine, eGFR using

MDRD, and 24-hours proteinuria are the tests mainly used in this indication. However, many monitoring schemes are available, current recommendations propose conflicting monitoring strategies, and sometimes modalities of the follow-up are not specified. These discrepancies can be explained because they are not supported by medical evidence. To date, the best monitoring strategy remains unknown and clear guidelines to standardize timing and tests to be performed are still lacking. Based on literature data we propose a kidney function monitoring strategy to guide physicians in this field. Serum creatinine, eGFR with MDRD equation, and 24-hours proteinuria should be used for this monitoring. A baseline assessment should be performed in all patients treated with 5-ASA. Then the monitoring timing should be carried out according to comorbidities, chronic renal disease, use of nephrotoxic drugs or concomitant steroid therapy. A tight monitoring may reduce morbidity and mortality of drug nephrotoxicity. Additional studies are needed to explore whether the kidney function monitoring has an impact on the occurrence of chronic kidney damage and end-stage renal disease related to 5-ASA.

Table and figures

Table 1: Monitoring schemes available in literature

Table 2: Current guidelines

Figure 1: Proposed strategy for kidney function monitoring in patients treated with 5-ASA

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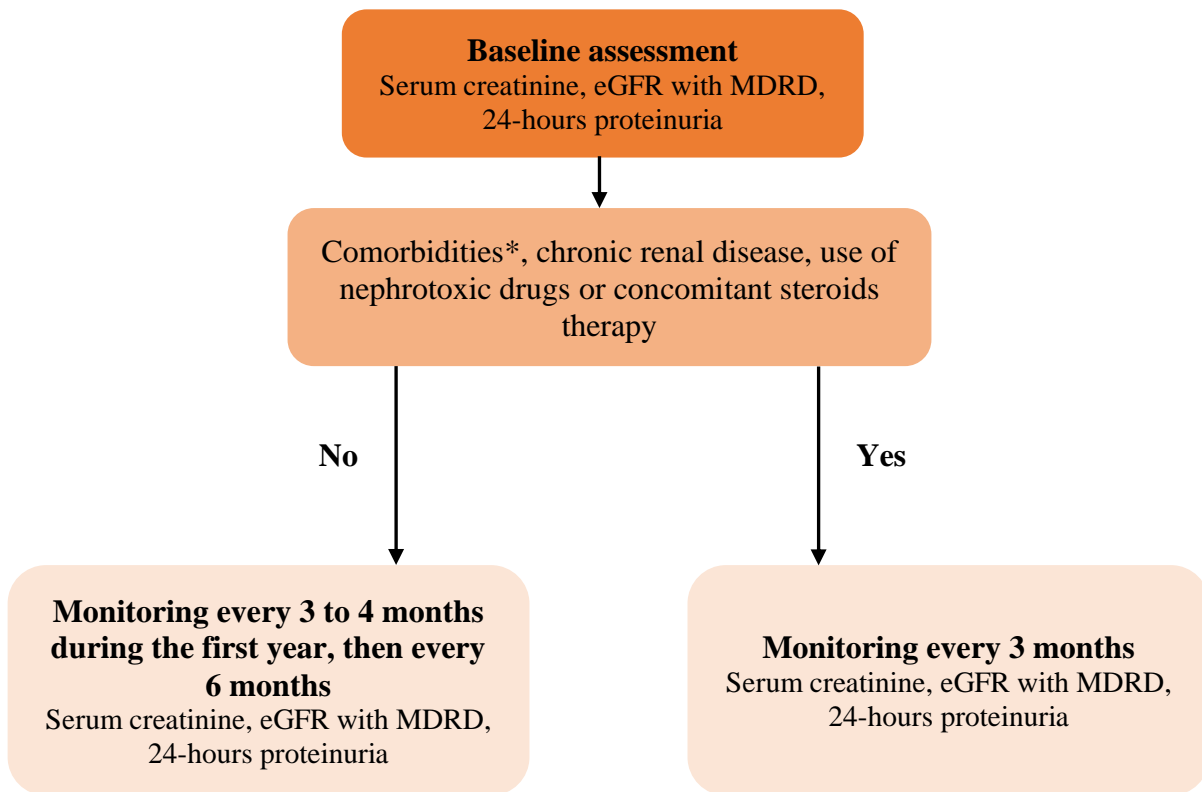
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Figure 1: Proposed strategy for kidney function monitoring in patients treated with 5-ASA



eGFR estimate glomerular filtration rate; MDRD, Modification of Diet in Renal Disease;

*Comorbidities: hypertension, diabetes

Table 1: Monitoring schemes available in literature

Authors	Frequency
Corrigan et al. ⁸	Baseline, monthly for the first 3 months, 3-monthly for the next 9 months, every 6 months, and annually after 5 years
Frandsen et al. ²⁵	Baseline, monthly for the first 3 months, 3-monthly for the next 9 months, then every 6 months
Cunliffe et al. ³³	At 6 and 12 months, then annually
Corica et al. ⁴²	At months 1, 3, and 6, then annually
Oikonomou et al. ⁴⁴	Every 4 weeks during the first 3 months, every 3 months for the first year, and then annually

Table 2: Current guidelines

Expert Group	Frequency	Tests
ECCO ^{20,26}	Every 3–6 months	Serum creatinine and full blood count
ACG ²⁷	At 3-6 months intervals during the first year, then annually	Serum creatinine
AGA ^{28,29}	Periodical monitoring of kidney function	Not specified
Toronto Ulcerative Colitis Consensus Group ³⁰	Baseline evaluation of kidney function and then periodically	Not specified
BSG ³¹	Baseline evaluation of kidney function, repeated after 2–3 months, then annually	Not specified
IG-IBD ⁶⁵	At 3-6 months intervals during the first year, then annually	Serum creatinine
GETAID expert group ⁶⁶	Every 6 months	Serum creatinine and 24-hours proteinuria
FDA ^{67,68}	Baseline and then periodically	Not specified

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; BSG, British Society of Gastroenterology; ECCO, European Crohn's and Colitis Organisation; FDA, Food and Drug Administration; GETAID, Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif; IG-IBD, Italian Group for the Study of Inflammatory Bowel Disease;