5-AMINOSALICYLATES AND RENAL FUNCTION MONITORING IN INFLAMMATORY BOWEL DISEASE: A NATIONWIDE SURVEY

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ABSTRACT

**Background and Aim:** 5-Aminosalicylates (ASA) are widely used in inflammatory bowel disease (IBD). Nephrotoxicity has been described in some IBD patients treated with 5-ASA. Whether physicians managing these patients are monitoring renal function in daily practice is unknown. We investigated how private gastroenterologists monitor renal function and manage renal failure in IBD patients treated with oral 5-ASA therapy.

**Methods:** This was a web-based cross sectional national survey which was conducted among private gastroenterologists.

**Results:** A total of 249 practitioners completed the survey. Eighty two per cent (n = 205) of responders declared that they always monitor renal function. The majority of gastroenterologists monitored twice a year glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease (MDRD) [90% (n = 225)] and Creatinine Clearance (CCr) using a 24-hours urine collection [51% (n = 126)]. Blood electrolytes, 24-hour urinary proteins rate and urinary strips are performed by 41%, 39% and 22% of practitioners, respectively. Before oral 5-ASA initiation, 59% (n = 148) of gastroenterologists screen for renal failure. In case of elevated creatinine levels, a nephrologic opinion is asked by 80% (n = 200) of responders and by 76% (n = 189) of gastroenterologists before treatment initiation.

**Conclusions:** Most gastroenterologists are monitoring renal function once or twice a year in IBD patients on 5-ASA. Less than two thirds of them screen for renal failure before treatment initiation. MDRD is mainly used, but a wide range of parameters are evaluated.

**Key Words:** 5-ASA, renal monitoring, renal failure, inflammatory bowel disease
INTRODUCTION

5-aminosalecylic acid (5-ASA) is recommended for both induction and maintenance therapy in ulcerative colitis (UC) at a dose from 1 to 4 grams per day. Therefore, 5-ASA are widely used in UC and more than half of patients’ are receiving oral 5-ASA treatment in the era of biologics. In a French referral center-based cohort, the probabilities of receiving oral mesalamine at 1 and 5 years from the time of UC diagnosis were 43.4% and 68.1%, respectively. In Crohn’s disease (CD), its efficacy remains controversial, but it is still used by some practitioners in this indication.

Nephrotoxic lesions due to high doses 5-ASA were first described in animal models. Chronic renal failure was reported in human receiving sulphasalazine and salicylazosulfapyridine since the 1970s. 5-ASA-related nephrotoxicity occurs particularly within the first 12 months, even if delayed presentations after several years have also been described. Such side effects usually take the form of an indolent, severe, chronic, and progressive interstitial nephritis. Restoration of renal function is leaded in 40%-85% of cases when the diagnosis is made within 10 months of starting treatment, thus suggesting the importance of an early biological diagnosis.

Patients with pre-existing renal impairment, concomitant potentially nephrotoxic drugs, or co-morbidities should benefit from a scheduled renal function monitoring during 5-ASA therapy. European Crohn’s and Colitis Organisation (ECCO) guidelines recommended creatinine and full blood count every 3-6 months in these patients. However gastroenterologists’ management of renal function during oral 5-ASA maintenance therapy in inflammatory bowel disease (IBD) patients in daily practice remains unknown.

We therefore performed a French national survey which aims at evaluating how private gastroenterologists monitor renal function and manage renal failure in IBD patients treated with oral 5-ASA therapy.
MATERIALS AND METHODS

Questionnaire

This was a web-based cross sectional national survey consisting of multiple-choice questions. The questionnaire was developed by the Nancy university hospital Departments of Gastroenterology (LPB, CZ and VB) and nephrology (LF) in close collaboration with a member (PF) of the French national association of private gastroenterologists, named CREGG (Club de Reflexion des cabinets et Groupes d'Hépato-Gastroentérologie). The questionnaire was developed based on available recommendations\textsuperscript{1-5,17} and after an exhaustive review of the literature.

The main section of the survey asked physicians to describe their monitoring practice for IBD patients receiving oral 5-ASA treatment. Specifically, they were asked to describe the types and frequency of monitoring tests performed. Physicians were also asked to describe their management of renal dysfunction before and during oral 5-ASA therapy. Of note, only physicians managing IBD patients were asked to respond to this survey.

The survey entitled « Renal function monitoring in IBD patients treated with oral 5-ASA » addressed the following 11 questions:

1. Do you monitor renal function of patients treated with oral 5-ASA?
2. If you monitor renal function, which biological tests are you using?
3. How often do you monitor Glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease (MDRD)?
4. How often do you monitor Creatinine Clearance (CCr) with collecting urine for 24-hours?
5. How often do you monitor blood electrolytes?
6. How often do you monitor 24-hour urinary protein?
7. How often do you monitor urinary strip?
8. Do you systematically evaluate renal function before starting oral 5-ASA treatment?

9. Which increase in the creatinine rate do you consider enough to cause treatment discontinuation?

10. Do you ask for a nephrologic opinion in case of increased creatinine level during oral 5-ASA treatment?

11. Do you ask for a nephrologic opinion before initiating oral 5-ASA treatment in patients with an abnormal renal function?

The survey was administered anonymously from March 2011 to July 2011. The questionnaire was consulting on the CREGG web-page. An email invitation to fill in the questionnaire was sent to all CREGG members with a second mailing to increase response rate.

**Statistical analysis**

The data were entered into a database (Microsoft Office Excel). Proportions were expressed as percentages.
RESULTS

Between March 2011 and July 2011, invitations to participate to the survey were addressed by e-mail to 1565 private gastroenterologists who are all CREGG members. A total of 249 practitioners responded to the survey and were included in the analysis.

Monitoring of renal function

Eighty two per cent (n = 205) of gastroenterologists declared that they always monitor renal function in IBD patients treated with oral 5-ASA. Only one percent (n = 3) of responders never follow renal function (Table 1).

Ninety per cent (n = 225) of gastroenterologists are evaluating Glomerular Filtration Rate (eGFR) using Modification of Diet in Renal Disease (MDRD) and 51% (n = 126) of them measure the Creatinine Clearance (CCr) using a 24-hours urine collection. Forty one per cent (n = 102) of responders are monitoring blood electrolytes. Practitioners are measuring the 24-hour urinary proteins rate and are using urinary strips in 39% (n = 96) and 22% (n = 54) of cases, respectively (Table 1).

Most of gastroenterologists monitor renal function-related parameters twice a year as 71%, 54%, 65%, 44%, and 39% of them declared evaluating MDRD, CCr, blood electrolytes, 24-hours urinary protein and urinary strips every 6 months, respectively (Figure 1).

Before starting 5-ASA oral treatment, 59% (n = 148) of gastroenterologists evaluated renal function and 29% (n = 72) of them never evaluated it (Table 1).
Management of renal dysfunction

An increase in the creatinine level from 30 to 50% leads to treatment discontinuation for 48% (n = 119) of gastroenterologists, whereas 29% of them stop therapy when a 10-30% increase in creatinine level is observed (Table 2).

In case of elevated creatinine levels while on 5-ASA therapy, a nephrologic opinion is asked by 80% (n = 200) of responders. In case of elevated creatinine levels before initiating 5-ASA therapy, a nephrologic opinion is asked by 76% (n = 189) of gastroenterologists (Table 2).
DISCUSSION

This is the first survey evaluating monitoring of renal function and management of renal failure in IBD patients on 5-ASA therapy.

Long-term 5-ASA therapy is generally considered to be safe and the occurrence of severe adverse effects is rare, with an incidence of 1 in 4000 patients/year. In a recent observational prospective study, renal impairment was observed in 2.2% of 1529 IBD patients, including both patients with and without concomitant 5-ASA treatment. Indeed, IBD patients not using 5-ASA are also at risk of renal disease. Guidelines recommended renal function monitoring. In the present survey, most of private gastroenterologists followed these guidelines as 82% of them declared always monitoring renal function in IBD patients under 5-ASA treatment.

A wide range of parameters is used for the screening of renal failure. The efficiency of urinary strips or electrolytes counts in identifying renal failure when use separately is uncertain. The adequate early marker of renal damage is not yet available. ECCO guidelines for IBD patients under 5-ASA therapy recommended creatinine and full blood count for patients with pre-existing renal impairment, concomitant use of other potentially nephrotoxic drugs, or co-morbid disease. Accordingly, practice guidelines in adults from American College of Gastroenterology recommended that serum creatinine should be measured periodically while on treatment. Half of practitioners used CCr collecting urine for 24-hours even though the superiority of this parameter is not established. This underscore the urgent need to develop international guidelines involving nephrologist experts. More studies are necessary to determine whether serum creatinine gives sufficient warning of nephrotoxicity or whether more elaborate tests of renal function are required. Such recommendations should also
define thresholds requiring treatment discontinuation, taking into account the IBD population particularities.

Most of respondents evaluate renal function-related parameters twice a year. Accordingly the Groupe d’Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID) recommended creatinine levels twice a year.\textsuperscript{22} About 50\% of reported cases of 5-ASA-induced interstitial nephritis present within 1 year of treatment initiation.\textsuperscript{14, 16, 23} American College of Gastroenterology recommended to monitor serum creatinine at 3–6 months intervals during the first year of mesalamine treatment, and then annually thereafter; the optimal monitoring schedule of serum creatinine in patients treated with mesalamine remains to be determined, as there is no evidence currently to suggest that the frequency of testing improves patient outcomes.\textsuperscript{21} Finally, there is still no evidence to date that either test, or the frequency of testing, is effective in identifying patients at risk of developing 5-ASA-related renal impairment.\textsuperscript{13} Given the large number of IBD patients treated with oral 5-ASA, further cost-effectiveness studies are also needed.

Surprisingly, whereas it is recommended to measure serum creatinine before initiating treatment with mesalamine or its prodrugs\textsuperscript{21}, only 60\% of practitioners evaluate renal function before starting 5-ASA treatment. Such baseline evaluation allows comparison with further values and should condition the initiation of a close monitoring under treatment.

It has been suggested that more attention may be needed for patients with chronic renal failure and IBD using 5-ASA.\textsuperscript{24} In our study, 76\% of gastroenterologists asked for nephrologic opinion before starting oral 5-ASA to those patients. There is a lack of data in the literature about the safety of 5-ASA compounds in IBD suffering from chronic renal failure.\textsuperscript{13} There are several limitations inherent to our survey. First, only 14.8\% of practitioners who have been mailed responded to the survey. Second, those who filled in the questionnaire
might be more aware of 5-ASA-related renal side effects. This could lead to an overestimation of renal function monitoring in our study. However, only physicians managed IBD patients were asked for survey. In addition, it is known that a total of 680 gastroenterologists are managing IBD patients in France.²⁵ Hence, it can be estimated that almost 40% of French gastroenterologists managing IBD patients responded to this survey. The strengths of our survey are the large number of responders and the fact that it was a nationwide survey. Finally, the survey account for real life practice as it concerned only private practice gastroenterologists.

In conclusion, the majority of gastroenterologists use to monitor renal function once or twice a year during long-term oral 5-ASA treatment while renal failure screening is performed to a lesser extent before treatment initiation. Most of practitioners screen all IBD treated patients without targeting at risk patients. MDRD is mainly used, but a wide range of parameters are evaluated. Cost-effectiveness studies as well as collaborative experts’ recommendations are keenly awaited in order to standardize renal monitoring and management in IBD patients receiving long-term oral 5-ASA treatment.

ACKNOWLEDGEMENTS We are grateful to all CREGG members who participated in the survey.

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FIGURE 1: Frequency and type of renal function monitoring

IBD, Inflammatory bowel disease; MDRD, Modification of Diet in Renal Disease; CCr, Creatinine Clearance; BE, Blood electrolytes; PROT, 24-hour urinary protein; US, urinary strip
REFERENCES


TABLE 1. Characteristics of renal function monitoring

<table>
<thead>
<tr>
<th></th>
<th>Number of respondents (n = 249)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of gastroenterologists who follow renal function</strong></td>
<td>243 (98%)</td>
</tr>
<tr>
<td><strong>Frequency of renal function monitoring</strong></td>
<td></td>
</tr>
<tr>
<td>- always</td>
<td>205 (82%)</td>
</tr>
<tr>
<td>- often</td>
<td>24 (10%)</td>
</tr>
<tr>
<td>- sometimes</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>- never</td>
<td>3 (1%)</td>
</tr>
<tr>
<td><strong>Number of gastroenterologists who perform a renal function evaluation before starting oral 5-ASA treatment</strong></td>
<td>148 (59%)</td>
</tr>
</tbody>
</table>

5-ASA, 5-aminosalicylic acid
### TABLE 2. Management of renal failure

<table>
<thead>
<tr>
<th>Increased creatinine rate leading in oral 5-ASA therapy discontinuation:</th>
<th>Number of respondents (n = 249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 10% to 30%</td>
<td>73 (29%)</td>
</tr>
<tr>
<td>- 30% to 50%</td>
<td>119 (48%)</td>
</tr>
<tr>
<td>- 50% to 70%</td>
<td>21 (8%)</td>
</tr>
<tr>
<td>- 70% to 100%</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>- more than 100%</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of gastroenterologists who ask for a nephrologic opinion in case of an increased creatinine rate during oral 5-ASA therapy:</th>
<th>200 (80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- always</td>
<td>109 (55%)</td>
</tr>
<tr>
<td>- often</td>
<td>41 (21%)</td>
</tr>
<tr>
<td>- sometimes</td>
<td>50 (25%)</td>
</tr>
<tr>
<td>- never</td>
<td>21 (8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of gastroenterologists who ask for a nephrologic opinion in case of an increased creatinine rate before starting oral 5-ASA therapy:</th>
<th>189 (76%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- always</td>
<td>85 (45%)</td>
</tr>
<tr>
<td>- often</td>
<td>49 (26%)</td>
</tr>
<tr>
<td>- sometimes</td>
<td>55 (29%)</td>
</tr>
<tr>
<td>- never</td>
<td>47 (19%)</td>
</tr>
</tbody>
</table>

5-ASA, 5-aminosalicylic acid