Drug-Induced Nephrotoxicity in Inflammatory Bowel Disease

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Key Words

Inflammatory bowel disease • Nephrotoxicity •
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inhibitors

Abstract

Conservative management of inflammatory bowel disease (IBD) is based on a combination of drugs, including aminosalicylates (ASAs), steroids, antibiotics, immunosuppressives and biologic agents. Although various side effects have been related to treatment regimens, drug-induced nephrotoxicity is rather uncommon. Furthermore, it is often underestimated since renal function deterioration may be attributed to the underlying disease. The nephrotoxicity of ASAs and cyclosporine A seems well established, but recent data have suggested a possible role of biologic agents such as infliximab and adalimumab in renal impairment. The aim of this review is to summarize the nephrotoxic effects of medical treatment as well as to express possible caveats in the administration of novel agents in IBD.

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Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) represent the two major forms of inflammatory bowel disease (IBD), affecting approximately 3.6 million people in

the USA and Europe [1]. IBD is often accompanied by several extraintestinal manifestations, occurring in 6–47% of IBD patients. Regarding renal and urinary involvement in particular, an incidence of 4–23% has been demonstrated. Nephrolithiasis, amyloidosis, tubulointerstitial nephritis (TIBN) and glomerulonephritis (GN) are considered as established manifestations, significantly correlated with bowel inflammation [2]. However, even when the above-mentioned entities are absent, microalbuminuria, as a sign of minimal renal dysfunction, may be present, reflecting disease activity [3].

Nevertheless, inflammation itself does not appear to be the only factor impacting renal function in IBD. Drug-induced nephrotoxicity is a rare but significant complication in IBD patients [4]. In order to evaluate the potential nephrotoxic drugs in IBD, pharmaceutical agents utilized to treat active disease and maintain remission should be mentioned [5]. Corticosteroids such as prednisolone and budesonide and antibiotics such as ciprofloxacin and metronidazole are considered as first-line therapy to induce remission in both UC and CD. Aminosalicylates (ASAs), including sulfasalazine and mesalazine, are associated with clinical improvement in active UC and are essential in maintaining remission; however, the efficacy of mesalazine is debatable in CD and seems to be beneficial only in mild ileocolonic disease. As second-line therapy, in order to achieve and maintain remission, thiopurines (azathioprine and 6-mercaptopurine) are effective in both UC and CD, whereas cyclosporine has a role in refractory UC and methotrexate in inducing re-

Table 1. Potential nephrotoxic effects of medical treatment in patients with IBD

Agents	Main nephrotoxic effects
5-ASAs	TIBN, GN
CsA, tacrolimus	renal vasoconstriction, interstitial fibrosis
TNF- α inhibitors (infliximab, adalimumab)	GN
Thiopurines (azathioprine, 6-mercaptopurine)	none, primary-collapsing glomerulopathy, acute kidney injury and severe nephrotic syndrome due to hematomphagocytic syndrome
Corticosteroids	none
Methotrexate	none at conventional doses
Mycophenolate mofetil	none
Antibiotics (mainly ciprofloxacin and metronidazole)	extremely rare events of TIBN related to ciprofloxacin
Total parenteral or enteral nutrition	none

mission and preventing relapse in CD [6]. Tumor necrosis factor- α (TNF α) inhibitors, such as infliximab and adalimumab, are efficacious in CD, while infliximab shows efficacy in UC, as well [7]. Among the aforementioned agents, ASAs, cyclosporine and TNF α inhibitors have been previously reported to affect the kidneys and provoke mild or severe renal impairment via different pathophysiological pathways [2]. Given the extensive utilization of these drugs, we attempted to highlight the impact of medical treatment on renal function of IBD patients. Table 1 summarizes potential nephrotoxic effects of pharmaceutical treatment administered to IBD patients.

Aminosalicylates

5-ASAs are the main therapeutic approach in IBD patients. Free 5-ASAs are unstable in acid and largely absorbed in the proximal intestine. Therefore, different formulations have been developed to induce 5-ASA absorption from the inflamed intestinal tissue. Both the combined form of sulfasalazine (5-ASA bound to sulfapyridine) and the coated form of 5-ASA (mesalazine, olsalazine) have been reported to be responsible for renal toxicity [8]. The established efficacy of 5-ASAs in inducing and maintaining clinical remission in IBD led to a

great number of trials concerning possible renal adverse events, which concluded that renal function may be directly affected by 5-ASA administration. Renal impairment may occur in up to 1 in 100 patients treated with 5-ASA, but clinically significant damage would occur in only 1 in 500 patients [3, 9].

Renal toxicity due to 5-ASA may present as GN, minimal-change nephropathy with nephrotic syndrome and interstitial nephritis, which may be associated with nephrogenic diabetes insipidus [10–17]. In many cases, it remains unclear whether renal impairment emerges as an extraintestinal manifestation or as an adverse drug effect. However, it is supported that 5-ASA may be causal in initiation of interstitial nephritis of patients with IBD. The subsequent reversal of this renal impairment, albeit partial, was temporally related to drug withdrawal [9, 18, 19].

A few cases of renal toxicity have been reported with sulfasalazine in the form of an idiosyncratic, dose-independent phenomenon occurring as a part of a generalized hypersensitivity reaction [20]. Mesalazine, on the other hand, has been reported to be responsible for a significant number of patients developing nephritis during its administration [21]. Mesalazine may provoke acute or chronic interstitial nephritis [13, 19, 22]. Patients with mesalazine nephrotoxicity show a striking male predominance [9]. Several clinical trials have reached the conclusion that TIBN in IBD patients during mesalazine treatment is not related to dosage or time of exposure, suggesting that cumulative exposure is not a significant factor for TIBN development [3, 8, 23] although a recent report by Patel et al. [24] suggests that a significant dose- and treatment duration-dependent decline of creatinine clearance is present in IBD patients. Symptoms such as malaise, fever, eosinophilia, skin rash may emerge as signs of TIBN, the absence of which, however, does not exclude 5-ASA nephrotoxicity. Renal biopsy can determine whether interstitial nephritis is the cause of renal deterioration [9].

The exact mechanism of induction of TIBN and the site of initiation within the kidney are not known. Only a minority of patients manifest a systemic type-1 hypersensitivity with fever and eosinophilia. Mesalazine is structurally related to salicylic acid and phenacetin, both of which are associated with the entity of ‘analgesic nephropathy’, which is characterized by interstitial nephritis and papillary necrosis. In the kidney, salicylate is both filtered and actively secreted by proximal tubules via the basolateral organic anion transporter. Passive reabsorption occurs throughout the nephron resulting in high cortical and medullary concentrations. Salicylates, inhibit the synthesis of intrarenal prostaglandins, which

are vasoactive mediators of intrarenal blood flow and uncouple oxidative phosphorylation in mitochondria. These effects, either alone or in combination with other events, cause a regional disturbance of intrarenal blood flow and local tissue hypoxia. High intrarenal concentrations of salicylate also inhibit the pentose phosphate shunt, reducing renal glutathione and rendering the kidney susceptible to oxidative damage. Ischemic reperfusion injury induces an inflammatory response at the endothelial level, causing inflammatory cell recruitment to local tissue. Tissue injury from recurrent hypoxia/reoxygenation, possibly related to peak plasma interstitial levels of salicylate exacerbated by reduced renal glutathione, could contribute to chronic inflammation and interstitial fibrosis. Direct tubular toxicity in addition to tissue hypoxia is also suggested [21].

The development of TIBN, either as an idiosyncratic response or as a nephrotoxic effect, suggests prompt discontinuation of 5-ASA therapy. The injury is usually reversible, but when diagnosis is delayed, it may be permanent [9, 13, 15]. Steroid or immunosuppressive therapy may improve renal dysfunction [9, 13, 14].

Although the mechanisms of 5-ASA nephrotoxicity have been analytically demonstrated, suggesting that renal function deterioration due to 5-ASAs is possible, a number of recent reports have shown IBD activity as the main factor responsible for renal impairment. Tubular proteinuria such as microalbuminuria has been demonstrated to be present in the majority of IBD patients, and seems to be related to disease activity rather than to 5-ASA treatment [25–32]. Even if users of 5-ASAs have an increased risk of renal disease, this risk may be partially attributable to the underlying disease. Furthermore, the incidence appears to be low and does not appear to be related to either the dose or type of 5-ASA used [25]. Regarding assessment of the renal function of IBD patients treated with 5-ASAs, it has been suggested that it should be monitored every 4 weeks during the first 3 months of 5-ASA therapy to identify patients who may be at risk of developing progressive renal damage. Monitoring can be reduced to 3-monthly for the first year and to yearly for the next years. Increased monitoring frequency is warranted in patients receiving steroid therapy since this may camouflage symptoms of significant renal damage during 5-ASA treatment [3, 9]. However, the optimal monitoring schedule in patients receiving 5-ASA treatment remains to be established as there is no evidence to date that either the test, or the frequency of testing, improves patient outcomes [3].

Cyclosporine

Cyclosporine A (CsA) is a neutral lipophilic cyclid peptide which interrupts the cellular immune response by inhibiting calcineurin and thus blocking mainly the production of interleukin-2 and interferon- γ by T-helper lymphocytes. It has been proposed as a rapid-acting alternative or adjunct to azathioprine or 6-mercaptopurine therapy in IBD [33]. Numerous trials attempted to clarify its efficacy in CD and UC, using as guide the proven efficacy of CsA in other immune-related diseases such as psoriasis and rheumatoid arthritis [34]. The results of these trials led to the suggestion that CsA is effective only in refractory fulminant UC [35–37] and severely active CD [34, 38–42].

Two approaches of CsA administration have been investigated; low-dose CsA (oral dose of ≤ 5 mg/kg/day) and high-dose CsA (oral dose of >5 mg/kg/day or intravenous dose of 4 mg/kg/day), which exhibited dose-related nephrotoxicity [43, 44]. Administration of low-dose CsA exhibited no serious nephrotoxicity [41], whereas side effects from high-dose CsA provoked renal impairment in 6% of patients [39, 43]. In all, patients undergoing CsA treatment for autoimmune diseases, including IBD, will have a 20% reduction in their glomerular filtration rate [45].

CsA can cause acute renal dysfunction by producing intense afferent arteriolar vasoconstriction, resulting in decreased renal blood flow and glomerular filtration rate and increases in serum creatinine [45]. Reduction or discontinuation of CsA usually improves renal function after 5–7 days [46]. There are many factors mediating CsA-induced vasoconstriction such as endothelin, thromboxane A₂, nitric oxide synthase inhibition and activation of the sympathetic nervous system, and their regulation demands appropriate pharmacologic maneuvers [45, 46].

Furthermore, CsA may provoke chronic renal impairment. It has been reported that histological evidence of nephropathy occurred in 21% of patients treated with oral CsA for autoimmune diseases revealing that manifested as striped interstitial fibrosis and tubular nephropathy in 15%; moderate to severe arteriolar alterations in 2%; or both in 5% [19]. The exact mechanism of chronic CsA nephrotoxicity remains unclear, although intrarenal activation of the renin-angiotensin system has been suggested to play a significant role [47].

Considering its nephrotoxicity in IBD patients, it has been suggested that CsA should be administered in doses <5 mg/kg/day [43]. However, a number of controlled trials in CD did not show a beneficial treatment effect

when low-dose CsA was administered. On the other hand, a few uncontrolled trials have suggested efficacy of high-dose CsA in active CD. In UC, although better results were shown with low-dose CsA, as well as greater efficacy at high doses, only 50% of patients will finally avoid colectomy. Given the higher rates of nephrotoxicity of high-dose CsA and its efficacy, previous reports conclude that short-term CsA administration (oral doses of >5 mg/kg/day or intravenous doses of 4 mg/kg/day) is advisable only in refractory UC [48, 49]. Monitoring of trough CsA levels is essential to prevent adverse events; trough CsA concentrations that occur during low-dose treatment are approximately 100–250 ng/ml, whereas for high-dose CsA they are approximately 250–400 ng/ml. The total duration of CsA therapy should not exceed 4–6 months, and treatment with another remission maintenance drug should be initiated. CsA dosages should be adjusted downward, whenever the baseline serum creatinine increases by >30%, while concomitant use of other nephrotoxic agents should be avoided, and patients with preexisting renal dysfunction probably should not be treated with CsA [43].

Tacrolimus, another calcineurin inhibitor with immunosuppressive properties similar to those of CsA has been considered as an alternative to CsA in IBD treatment. In a small number of trials, administration of 0.1–0.2 mg/kg of oral tacrolimus in order to achieve blood levels between 5 and 15 ng/ml in patients with refractory IBD demonstrated average efficacy, suggesting that it may be used as bridging therapy. However, tacrolimus has also exhibited nephrotoxic effects similar to CsA [50, 51].

TNF α Inhibitors

TNF α is a proinflammatory cytokine that plays an important role in the intestinal inflammation of IBD patients. Thus, its inhibitors, particularly infliximab (a chimeric anti-TNF IgG1 monoclonal antibody) and adalimumab (a recombinant anti-TNF IgG1 monoclonal antibody), and, to a lesser extent, etanercept (a recombinant dimer of human TNF receptor proteins fused and bound to human IgG1 that acts competitively to inhibit the binding of TNF to its cell surface receptor) were evaluated in the treatment of CD. However, recent studies showed increased levels of TNF α in serum and stool of patients with UC, findings that led to clinical trials of TNF α inhibitor administration to patients with active UC [52]. Although TNF α inhibitors showed great effi-

cacy in inducing and maintaining clinical remission in IBD – infliximab and adalimumab in particular, but not etanercept – they are not without serious adverse effects [53, 54].

TNF α inhibitor efficacy in several autoimmune diseases, such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, and IBD led to different observations [55]. Although previous reports suggested a possible beneficial role of TNF α inhibitors in the treatment of GN [56–59], more recent reports and greater experience with TNF α inhibitors raised intriguing questions concerning the efficacy of TNF α inhibitors in GN as well as demonstrating a possible causative role in the emergence of renal complications such as GN. To our knowledge, GN occurred in at least 19 patients (most of them developing lupus nephritis), during treatment with anti-TNF α [60–68], as indicated in table 2.

Despite the paucity of data regarding GN in IBD patients as complications of TNF α inhibitor therapy, recent reports supporting a triggering role of TNF α inhibitors in renal impairment suggest an important adverse effect [69]. A possible mechanism responsible for the development of renal complications during anti-TNF α administration implicates an interaction of anti-TNF α antibodies with TNF α present on glomerular visceral epithelial cells [60]. It has also been proposed that binding of infliximab to TNF α on the lymphocyte plasma membranes might induce apoptosis, releasing immunogenic nucleosomal antigens that promote anti-dsDNA antibody formation [69]. Moreover, the induction of antinuclear antibodies, anti-dsDNA and antineutrophil cytoplasmic antibodies from TNF α inhibitors may give rise to either lupus-like immune complex GN or antineutrophil cytoplasmic antibody-related necrotizing and crescentic GN in susceptible individuals [70]. The temporal relation of new-onset glomerular disease to drug use, the improvement of clinical symptoms and laboratory abnormalities after drug withdrawal and the administration of immunosuppressive therapy in the majority of patients show that renal complications following the administration of TNF α inhibitors were not coincidental.

Other Agents and Nephrotoxicity in IBD

In addition to the above-mentioned medical treatments, other agents used in IBD therapy, such as corticosteroids, thiopurines (azathioprine and 6-mercaptopurine), methotrexate and mycophenolate mofetil, showed

Table 2. TNF α inhibitor-associated renal complications

Underlying disease	TNF α inhibitors	Renal complication	Cases	Authors
Rheumatoid arthritis	Adalimumab	Glomerulonephritis	1	Den Broeder et al. [61]
Rheumatoid arthritis	Infliximab	Glomerulonephritis	2	Chin et al. [62], Stokes et al. [63]
Rheumatoid arthritis	Etanercept	Glomerulonephritis	4	Kemp et al. [64], Stokes et al. [63]
Rheumatoid arthritis	Adalimumab	Lupus nephritis	1	Stokes et al. [63]
Juvenile idiopathic arthritis	Etanercept	Lupus nephritis	2	Stokes et al. [63], Mor et al. [65]
Psoriatic arthritis	Etanercept	Glomerulonephritis	1	Doulton et al. [66]
Psoriatic arthritis	Etanercept	Lupus nephritis	1	Haake et al. [67]
Rheumatoid arthritis or ankylosing spondylitis	Undefined	Glomerulonephritis	2	Saint Marcoux et al. [68]
Rheumatoid arthritis or Crohn's disease or ankylosing spondylitis or psoriatic arthritis or juvenile idiopathic arthritis	Etanercept or infliximab or adalimumab	Lupus nephritis	5	Ramos-Casals et al. [69]

Review of the literature identified 19 cases with severe renal parenchymal complications during therapy with TNF α inhibitors.

no direct significant effects on renal function. Methotrexate, in particular, although showing potential nephrotoxicity when administered in high doses, exhibited no nephrotoxic effect in conventional doses used in IBD [71]. Regarding azathioprine, no evidence of a direct renal effect has been identified. However, prolonged azathioprine treatment in IBD patients may provoke renal impairment due to development of the hemophagocytic syndrome. The hemophagocytic syndrome, which is caused by excessive activation and proliferation of non-malignant macrophages, may be triggered by cytomegalovirus, parvovirus or herpes simplex virus infection in immunosuppressed patients such as IBD patients receiving azathioprine. The hemophagocytic syndrome may be accompanied by collapsing glomerulopathy, acute kidney injury and severe nephrotic syndrome [72–74]. Finally, extensive administration of antibiotics such as ciprofloxacin and metronidazole as well as utilization of total parenteral or enteral nutrition do not appear to cause renal impairment although a few case reports have suggested ciprofloxacin-related nephrotoxic effects [75].

Conclusions

Among ‘older’ and ‘novel’ agents utilized in the management of IBD, chiefly ASAs, CsA and biologic agents are potentially nephrotoxic drugs. Since bowel inflammation usually overshadows renal signs and symptoms, it may be difficult to identify the exact cause of renal function deterioration. There is a thin line between renal dysfunction as an extraintestinal manifestation and renal

injury due to medical treatment which cannot always be drawn. Furthermore, the steadily increasing utilization of TNF α inhibitors in IBD demands higher degree of vigilance. Although most experience concerning TNF α inhibitor nephrotoxicity has been gathered from other autoimmune diseases, their potential role in renal damage of IBD patients cannot be ignored. Nevertheless, watchfulness and monitoring of renal function can lead us to early diagnosis, whereas prompt discontinuation of toxic medical treatment is essential to prevent further damage and in many cases fully reverse renal injury.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Editorial Comment

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This comprehensive review by Oikonomou and colleagues highlights the renal complications of the treatment of inflammatory bowel disease (IBD). Whilst most nephrologists would be familiar with the risks associated with short- and long-term use of 5-aminosalicylates (5-ASAs) containing compounds such as sulphasalazine and mesalazine, they need to become aware of the potential nephrotoxicity of newer therapies such as anti-TNF- α treatment. Also, the authors point to the often encountered difficulties related to determining whether renal dysfunction in patients with IBD is caused by extra-intestinal manifestations of the disease or by complications of the treatment. For instance, interstitial nephritis can be caused by either. A thorough clinical evaluation as well as detailed renal histology may guide clinicians. Unfortunately, there are no official guidelines on renal function monitoring in IBD patients. Patients not receiving treatment should be monitored annually. It would be advisable to monitor renal function at regular intervals (every

3 months) after initiation of 5-ASAs. Monitoring should include urine albumin excretion rate as well as serum creatinine measurement and estimated GFR (eGFR). Caution should be exerted in interpreting these results in patients with IBD. Microalbuminuria has been associated with disease flare-ups, is often transient and regresses during quiescent phases. It may reflect the systemic inflammatory response of the vascular endothelium to the disease. eGFR levels may be confounded in patients with IBD and wasting by sarcopenia and associated decreased serum creatinine levels and falsely raised eGFR. Most eGFR formulations correct poorly for changes in body muscle mass. Overall, close monitoring of renal function in patients with IBD is warranted probably through closer coordination between gastroenterologists and nephrologists. Also, improved education of general physicians caring for these patients relating to monitoring of renal function is warranted.