PharmacologyOnLine August 30, 2015

Newsletter • 2015 • vol.2 • 1-9

INFLAMMATORY BOWEL DISEASE: HOW CAN TRADITIONAL THERAPY HELP?

Souza, M.S.S.[1*]; Barbalho, S.M.[2]; Goulart, R.A.[3]; Carvalho, A.C.A.[4]

[1]Department of Biochemistry and Pharmacology, School of Medicine, University of Marília, Higino Muzzi Filho Avenue, 1001, Marília – SP- Brazil;
[2]Department of Biochemistry and Pharmacology, School of Medicine, University of Marília and Food Technology School (FATEC), Higino Muzzi Filho Avenue, 1001, Marília – SP- Brazil.
[3]Department of Gastroenteology, University Hospital - UNIMAR, Higino Muzzi Filho Avenue, 1001 - Marília – SP- Brazil,
[4]Diagnostic Center in Gastroenterology, Arthur Sampaio Street, 140, Ibaiti – PR- Brazil

*maricelma.soares.souza@gmail.com

Abstract

The alterations in the bacterial species residing in the gastro-intestinal tract promote a response from the immune system. This response will result in inflammatory processes that are related to the pathology of many diseases, including inflammatory bowel disease (IBD). The two main forms of IBD are known as Crohn's Disease (CD) and Ulcerative Colitis (UC) that differ clinically in the bowel location, nature, and the histological patterns of the inflammatory lesions as well as the association with imbalance of the host's immune response. These pathologies require suitable treatment strategies and the ttherapy for IBD has not changed deeply in the past 4-5 decades and still uses nonsteroidal anti-inflammatory drug 5-ASA and its colon-targeting prodrug sulfasalazine followed by second-line treatment with steroids and immunomodulators. Aminosalicylates include sulfasalazine, which constitutes 5-ASA (mesalazine) linked to sulfapyridine by an azo bond. Thiopurines used are azathioprine (AZA), 6-mercaptopurine (6-MP) and occasionally also 6-thioguanine. Corticosteroids have represented the mainstay of medical therapy in active inflammatory bowel disease. The use of TNF monoclonal antibody, recombinant anti-inflammatory cytokines, and related gene therapy are recent advances in the field. Anti TNF-α agents include infliximab, adalimumab, certolizumab. Methotrexate is also an effective medication for treating a variety of inflammatory diseases, including IBD. These drugs allow an extension in the expectation and the quality life of the patients.

Keywords: Inflammatory Bowel Disease, Anti-TNF, corticosteroids, aminosalicylates

Introduction

The gastro-intestinal tract microbiota interacts with the host in order to help in the balance of physiological processes and consequent maintenance of homeostasis. A response from the immune system is triggered when this balance in the bacterial species residing in the gastro-intestinal tract is altered. This response will result in inflammatory processes that are related to the pathology of many diseases, including inflammatory bowel disease (IBD). The disorders in the gastrointestinal (GI) system are characterized by recurrent inflammation, with periods of relapse and remission, and epithelial injury [1-3].

The innate immune system is the first line of defense against microorganisms to which the body is exposed daily and is involved in the protection of the organism by responding appropriately to the pathogenic bacteria. Initially there is a nonspecific response of macrophages, dendritic cells and granulocytes, and this process is related to the activation of Pattern Recognition Receptors (PRRs) that are able to recognize pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns. In homeostasis the PRRs may exhibit a successful acute inflammatory response leading to the elimination of the bacteria and consequent resolution of inflammation and tissue repair. This is an acute inflammation process that is a necessary condition to recover the homeostasis but when control is lost it leads to a chronic state that characterizes the IBD. Chronic inflammation may increase tissue damage, epithelial cell necrosis and the subsequent release of DAMPs that can activate Toll-like receptors (TRL) that is a PRRs type related to UC and CD. TRL protect the extracellular space and Nucleotide oligomerization domain like receptors that protect the intracellular cytosolic compartment. For antigen recognition, there is a recruitment of cellular kinases which trigger the activation of signaling cascades leading to activation of MAPK pathways (mitogen activated kinase) and Nuclear factor-κ β (NF-kappa β). In the intestine these receptors are distributed and have particular functions in the pattern of the immunological response [4-8].

Toll-like receptors activation induce autophagy and incapacity to distinguish pathogenic and commensal bacteria leading to the activation of nuclear factor kappa beta (NFκB), that triggers overproduction of inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin 1β (IL-1β). The consequences of these inflammatory processes include pain, bleeding, modifications on the bowel habits, and increases risk of bowel cancer [8-12]. The two main forms of IBD are known as Crohn's Disease (CD) and Ulcerative Colitis (UC). These forms are the main clinical phenotypic manifestations of the inflammatory disease. UC and CD are clinically different in the bowel location, nature, and the histological patterns of the inflammatory lesions as well as the association with imbalance of the host's immune response.

They usually manifest in genetic susceptible people and are linked to an environmental trigger that provokes an immune response in the intestinal mucosa. The causes and pathogenesis of UC and CD are not totally understood but it is known that there is an increase in the inflammatory markers and in the oxidative stress beyond the colonic disarrangement. They can cause significant morbidity with increased mortality and they require lifelong treatments and strategies that prolong the expectation and the quality life of the patients [3, 13-16]. UC normally is represented by an unending inflammation process in the colonic mucosa which extends from the rectum and rarely affects the colon and terminal ileum and its distribution is stratified by the colonic extension involved. In the other hand, CD may affect any part of the GI system (from mouth to anus) and it differs from UC because of the skip patterns of the lesions where it is possible to find regular areas separated from inflammatory areas. Both diseases can undergo to remission and flare periods [12, 14, 17, 18].

IBD can be related to the modern society. There are evidences that the incidence is higher in developed countries and it may be associated with excessive consumption of fats, sugars, food additives and restriction of fibers. It is still controversial that psychological aspects and stress is a trigger for the recurrence of these disorders. Reduction of the exposure to infections during childhood would result in an inappropriate immune response when exposed to infections at later stages of life and would take to vulnerability to develop IBD.

Other environmental factors may be related to the manifestation of IBD. Cigarette smoking appears to protect against UC but would be related to increase incidence of CD. Appendectomy seems be a preventive factor for UC. Previous episodes of GI infections of *Salmonella spp*, *Shigella spp* and *Campylobacter spp* increase the risk of subsequent development of UC suggesting that a previous infection can modify the intestinal flora in genetically predisposed patients and triggers inflammation [19-21]. A better understanding of the deleterious immune response helped the development of anti-TNF-α therapy, and other series of biologic agents

which modified the therapeutic approach of the patients. Authors have shown that a long-term remission of the disease requires mucosal healing and epithelial cells show an important paper in this matter. It is also important to point that both CD and UC may be related to a significant morbidity with increased mortality and requires lifelong treatments that extend patient´s life quality [13, 22].

Methods

This review brings the importance conventional therapy in the treatment and maintenance of remission in IBD patients. It was based on a research of articles related to IBD and the drugs used to the treatment. The following databases were used: Pubmed, Medline, Scielo, Scopus and Lilacs in order to find relevant clinical trials or epidemiological studies and reviews limited to indexed scientific articles involving humans and animals.

Traditional Pharmacologic Therapy

Recently, substantial advances in the understanding of the molecular pathogenesis of inflammatory bowel disease (IBD) have been made owing to three related lines of investigation. First, IBD has been found to be the most tractable of complex disorders for discovering susceptibility genes, and these have shown the importance of epithelial barrier function, innate and adaptive immunity in disease pathogenesis. Second, efforts directed towards the identification of environmental factors implicate commensal bacteria (or their products), rather than conventional pathogens, as drivers of dysregulated immunity and IBD.

Third, murine models, which exhibit many of the features of ulcerative colitis and seem to be bacteria-driven, have helped unravel the pathogenesis/mucosal immunopathology of IBD. Therefore CD and UC have similar GI and extraintestinal manifestations and respond to similar drugs, though current evidence suggest that these disorders are the result of the fundamentally different pathogenetic mechanisms which may cause different levels of efficiency to the pharmacological therapy [23]. Most IBD patients are treated with conventional medical therapy, because emerging therapies for IBD are regulated by health-care jurisdiction and often limited to academic centres. Some patients may suffer from serious side-effects or toxicities from these conventional therapies, including aminosalicylates, corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, infliximab and adalimumab [24].

Aminosalicylates

The archetype of this group of drugs is sulfasalazine, which possesses 5-ASA (mesalazine) linked to sulfapyridine by an azo bond (Figure 1). Therapy for IBD has not seen major changes or breakthroughs during the past 4-5 decades and still revolves around the nonsteroidal anti-inflammatory drug 5-ASA and its colon-targeting pro-drug sulfasalazine followed by second-line treatment with steroids and immunomodulators, because reducing the extent and severity of colonic inflammation remains the primary focus of treatment [25].

The anti-inflammatory mechanism by which the aminosalicylates exert their therapeutic action is not well established but several hypotheses have been documented. 5-ASA is a potent inhibitor of arachidonic acid metabolism, decreasing the synthesis of both leukotrienes and prostaglandins. Moreover, 5-ASA is a potent scavenger of free radicals [26]. This drug acts via NF-κB and TNF-α inhibition [27]. These findings suggest that the use of either drug in IBD may decrease the heightened state of *lamina propria* lymphocyte activation as a part of their therapeutic action [28]. Mesalazine formulation with delayed action is released throughout the small intestine and colon, while the pH sensitive mesalazine is released in the terminal ileum and large intestine (Figure 2).

These differences in the release areas have important therapeutic implications drug [29]. The most frequent adverse effect of 5-ASA is GI disturbance, including nausea, vomiting, abdominal pain and diarrhea. Occurrence of peptic ulcers and gastric hemorrhage is rare. Decreased absorption of vitamin $B_{12,}$ folic acid, iron and lipids is also observed. Adverse GI effect can be minimized in patients by administration of the drug with food or discontinuation of the drug when symptoms are severe [30].

Cyclosporine

Cyclosporine (CsA) is a fungal cacineurin inhibitor which was isolated from a fungus (*Tolypocladium inflatum*) and can prevent the transcription of mRNA encoding interleukine-2, thus CsA interferes with mucosal inflammation [31]. Approximately 25% of fulminant UC patients are steroid-refractory which is defined as the loss of response to treatment with IV steroid [32]. Many studies have shown the efficacy of CsA as a short term “rescue therapy” in steroid-refractory UC patients [33, 34]. Commom side effects

of CsA include nephrotoxicity, hypertension, seizure, opportunistic infections, peripheral neuropathy, anaphylaxis, colonic perforation, increased postoperative mortality, hirsutism and headache [35, 36].

Thiopurines

Thiopurines used for inflammatory bowel disease (IBD) treatment are azathioprine (AZA), 6-mercaptopurine (6-MP) and occasionally also 6-thioguanine (6-TG). The most commonly used thiopurine is AZA. The hepatic enzyme glutathione-S-transferase rapidly cleaves the pro-drug AZA to 6-MP [37]. which is then metabolized in both liver and gut by several enzymes: (1) thiopurine-s-methyltransferase (TPMT) catalysing 6-MP to 6-methyl-MP (6-MMP); (2) xanthine oxidase catalyzing 6-MP to thiourea; and (3) hypoxanthine-guanine-phosphoribosyltransferase converting 6-MP to 6-thioguanine nucleotides (6-TGN). 6-TG is the final effector-metabolite which slowly accumulates in cells, and this metabolite is probably responsible for the delayed onset of action after 10-12 weeks [38, 39]. The cytotoxic thiopurine derivatives known as mercaptopurine (6-MP) and azathioprine are used to treat patients with severe inflammatory bowel disease, or resistant or dependents of corticosteroids [40]. These antimetabolites thiopurine suppress the biosynthesis of purines and inhibit cell proliferation. The two drugs are pro-drugs. The azathioprine is converted into mercaptopurine which is then biotransformed to 6-thioguanine nucleotides, most likely the active molecule (Figure 3).

Thiopurine therapy is usually introduced as steroid-sparing therapy in UC when a patient's condition fails to respond to two courses of steroid therapy. In addition, certain clinical scenarios such as presentations of acute severe colitis treated with rescue therapy may require early thiopurine therapy to maintain remission. Thiopurines are generally used earlier in CD as they provide long-term disease course modification which steroid therapy does not provide. A recent prospective study concluded that early azathioprine (AZA) therapy (within 8 weeks of diagnosis) provided no benefit in sustaining steroid-free remission compared with placebo [41].

Thiopurine therapy should be personalized and tailored to the individual being treated. Its metabolism remains complex but it is important to understand and identify reasons to why a thiopurine is ineffective or not tolerated. Dose changes, switching to another thiopurine/drug, allopurinol co-prescription and management of side effects are crucial to ensure these drugs are used in the best way [42]. The major dose-dependent side effect of thiopurines is drug-induced myelosuppression which is observed in 2%-5% of Caucasian patients [43]. Hepatotoxicity can manifest as early drug-induced hepatitis, nodular regenerative hyperplasia after years of therapy, sinusoidal dilatation or fibrosis [44]. Pancreatitis is an important idiosyncratic side effect and occurs in up to 4% of the patients especially during the first weeks of treatment [45]. The most frequent idiosyncratic side effects are nausea, vomiting, and malaise in up to 15% of all patients [46].

Corticosteroids

For more than 50 years, corticosteroids (CS) have represented the mainstay of medical therapy in active inflammatory bowel disease [47]. Natural and synthetic glucocorticoids (GCs) are widely employed in a number of inflammatory, autoimmune and neoplastic diseases, and, despite the introduction of novel therapies, remain the first-line treatment for inducing remission in moderate to severe active CD and UC [48]. Free glicocorticosteroids are able to diffuse passively across plasma membranes and interact specifically with a cytosolic receptor (GR), expressed in virtually all tissues.

The GC receptor is a member of the nuclear receptor (NR) superfamily, which includes receptors for steroid hormones (e.g. corticosteroids, androgens, estrogens and progesterone), as well as other hydrophobic molecules (such as bile acids, vitamins A and D, retinoic acid and thyroid hormones). All these molecules induce their actions by the same molecular mechanism: at the basis of this mechanism stands the physical interaction between the lipophilic ligand and its own cytosolic/nuclear receptor that, in turn, activates a multistep signal transduction pathway to end up in specific genomic transcriptional effects [49]. The molecular mechanisms of GC action are further complicated by the realization that these hormones can also induce rapid non-genomic effects within the cytoplasm; for example, they induce the release of Src kinase from the GR heterocomplex, which results in lipocortin activation and inhibition of arachidonic acid release [50], and altered cytoplasmic ion content [51]. HO et al. [51] demonstrated that eighty-six (63%) with UC and 60 (75%) with CD patients required treatment with corticosteroids. In UC, 64 (74%) and 22 (26%) patients were started on oral and intravenous CSs respectively. Sixty (75%) patients with CD were initially treated with CSs. Of these, 52 (87%) and

eight (13%) patients were started on oral and intravenous CSs respectively. Only one patient was treated with intravenous ciclosporin in this study. Although corticosteroids are effective, dependence/resistance remains common. Patients with extensive ulcerative colitis and fistulizing/stricturing Crohn's are most at risk of failing corticosteroid therapy [51]. In consideration of the complexity of GC mechanisms of action, the most common forms of resistance observed in chronic inflammatory conditions, and in IBD in particular, may occur at several levels, and some candidate areas have been identified: (1) the GR receptor heterocomplex and proteins involved in nuclear translocation and transcription; (2) the pro-inflammatory mediators in the downstream signaling pathway of the GCGR complex; and (3) P-glycoprotein (P-gp) and other proteins involved in the extrusion and metabolism of GCs [48].

This fact contributes to the increasing morbidity secondary to both continually active disease and prolonged exposure to CS therapy [53, 54]. In this context, the use of immunosuppressants, such as azathioprine/mercaptopurine (6-mercaptopurine) and methotrexate are also firmly established [55, 56]. In the recent years, there has been an expansion of biological therapies, in particular, monoclonal antibody therapy directed against TNF, such as infliximab in CD [58] and more recently in UC together with nutritional therapies [59]. The systemic effects of corticosteroids high doses of use or prolonged therapy for each include addition to suppression of the hypothalamic-pituitary-adrenal, electrolyte abnormalities, hypertension, hyperglycemia, osteoporosis, myopathy, cataracts, stretch marks, ecchymoses and susceptibility to infections [29].

Biological agents

The common therapies for CD are aminosalicylates, steroids, immune suppressants and monoclonal antibodies. Aminosalicylates such as mesalamine and sulfasalazine are used to treat mild to moderate CD [60] while corticosteroids are used to treat acute active CD and patients who do not respond to aminosalicylates. However, the use of corticosteroids has a high risk of Cushing's syndrome, infection and diabetes in the short term, and bone loss, increased ocular pressure and diabetes in the long term [61]. Immunosuppressants are used to inhibit inflammation and their long-term use may cause infection, liver toxicity and bone marrow suppression [62]. The use of TNF monoclonal antibody, recombinant anti-inflammatory cytokines, and related gene therapy are recent advances in the field [63]. Anti TNF-α agents include infliximab, adalimumab, certolizumab. They are effective in inducing and maintaining clinical remission, inducing mucosal healing, improving quality of life, and reducing the risk of hospitalization and surgery in adult and pediatric patients with CD [64]. Current studies were found that the migration of leukocytes and other inflammatory cells into the intestinal vasculature and disruption of intestinal barrier function were important in the pathogenesis of CD. Therefore the integrin antagonists (natalizumab and vedolizumab) aim to block the interaction between leukocytes and endothelial cells to inhibit inflammation [65, 66]. A recent meta-analysis compared the efficacy of adalimumab (human monoclonal antibody) and infliximab (chimeric monoclonal antibody) in the treatment of moderate to severe UC assessing clinical remission, clinical response, mucosal healing, quality of life, serious adverse events and discontinuation due to adverse events at week 8 and at week 52. However, the comparison of these studies is difficult because, although the study setting and clinical context are similar, the study protocols and primary outcomes are different [67].

To summarize the immense information concerning adverse events and safety issues the Austrian Society of Gastroenterology and Hepatology launched this evidence based consensus on the safe use of infliximab which covers the following topics: infusion reactions and immunogenicity, skin reactions, opportunistic infections (including tuberculosis), non-opportunistic infections (bacterial and viral), vaccination, neurological complications, hepatotoxicity, congestive heart failure, haematological side effects, intestinal strictures, stenosis and bowel obstruction (SSO), concomitant medication, malignancy and lymphoma, IFX in the elderly and the young, mortality, fertility, pregnancy and breast feeding [68]. As with all anti-TNF agents, adalimumab and infliximab are immunogenic, and some patients receiving long-term these drugs will develop anti-drug antibodies, causing a loss of response [69].

Methotrexate

Methotrexate is a medication that is effective for treating a variety of inflammatory diseases. In IBD methotrexate's clinical efficacy has been established for steroid-dependent CD in adults and also in children refractory or intolerant to thiopurine therapy [69, 70]. The classic mechanism of action of

this drug is an analog of folic acid and of aminopterin, which is also a folic acid antagonist. One of the main mechanisms of its action is the inhibition of dihydrofolate reductase, the enzyme involved in the synthetic pathway for purines and pyrimidines. The underlying anti-inflammatory effect of low-dose methotrexate in inflammatory diseases such as rheumatoid arthritis, psoriasis, and IBD is less clear, as the anti-proliferative activity of low-dose methotrexate is minimal. Multiple mechanisms of actions are proposed, including promotion of adenosine release, inhibition of production of pro inflammatory cytokines, suppression of lymphocyte proliferation, reduction of neutrophil chemotaxis, and adherence and decrease of serum immunoglobulins [71, 72]. Moderate quality evidence indicates that intramuscular methotrexate at a dose of 15 mg/week is superior to placebo for maintenance of remission in CD and the intramuscular administration seems to be safe. Low dose of oral methotrexate (12.5 to 15 mg/week) does not seem to be effective for maintenance of remission in CD. Combination therapy (methotrexate and infliximab) does not appear to be any more effective for maintenance of remission than infliximab monotherapy. The results for efficacy outcomes between methotrexate and 6-mercaptopurine and methotrexate and 5-aminosalicylic acid were uncertain [73].

Concomitant use of immunomodulators like methotrexate, azathioprine, and 6-mercaptopurine often increases the systemic exposure of the anti-TNFα agent and decreases the formation of antibodies to the anti-TNFα agent, consequently enhancing clinical efficacy. Nevertheless, long-term combination therapy with immunomodulators and anti-TNFα agents may be associated with increased risks of serious infections and malignancies. Therefore, the determination whether combination therapy is suitable for a patient with CD should always be based on an individualized benefit-risk evaluation [74]. The most common side effects of MTX include nausea, anorexia, stomatitis, diarrhea, hepatotoxicity, bone marrow suppression and hypersensitivity pneumonitis and opportunistic infections [75].

Conclusion

IBD are disorders in the gastrointestinal system characterized by recurrent inflammation and related to morbidity and increased mortality and require lifelong treatments to improve and extend patient´s life quality. The clinical treatment of IBD is not simple. As there are many factors involved, the modern treatment seeks to reduce the generalized inflammatory response, however, no drug can provide this effect to all patients, and the response obtained in a given case with a specific drug can be unpredictable and unsatisfactory. Recent genome studies revealed many genes associated with IBD, which identification can lead to the development of new treatments, ie, new therapeutic approaches.

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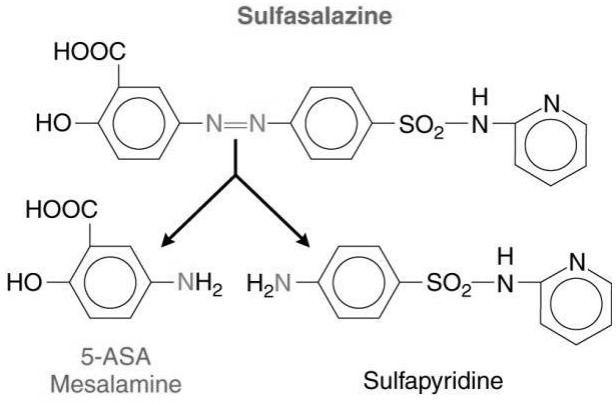

Figure 1. Structures of sulfasalazine and related agents. The N atoms indicate the diazo linkage that is cleaved to generate the active moiety (Adapted from *Goodman* & *Gilman's* The Pharmacological Basis of Therapeutics, 12e. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann) [29].

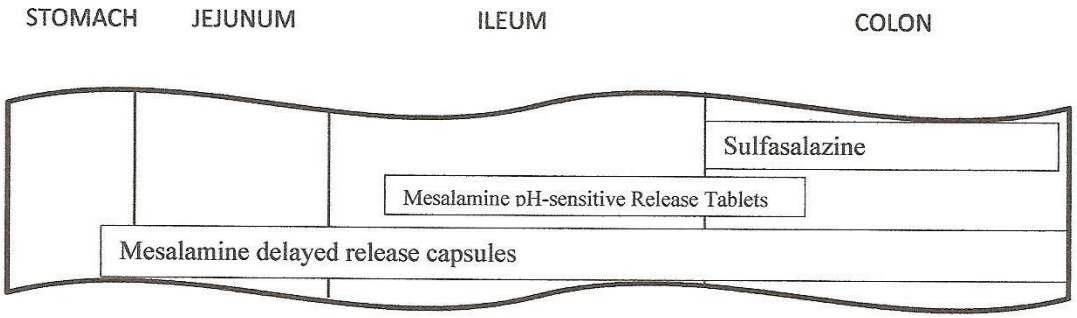

Figure 2. Sites of release of mesalamine (5-ASA) in the gastrointestinal tract from different oral formulations. (Adapted from *Goodman* & *Gilman's* The Pharmacological Basis of Therapeutics, 12e. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann) [29].

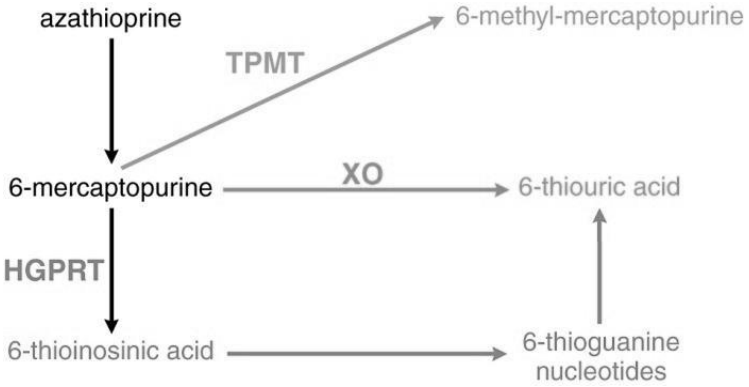

Figure 3. Metabolism of azathioprine and 6-mercaptopurine. TPMT, thiopurine methyltransferase; XO, xanthine oxidase; HGPRT, guanine-hypoxanthine phosphoribosyltransferases. (Adapted from *Goodman* & *Gilman's* The Pharmacological Basis of Therapeutics, 12e. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann) [29].