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New Horizons in Management of Inflammatory Bowel Disease

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Inflammatory Bowel Disease (IBD)-a chronic debilitating gastrointestinal (GI) disease- may affect any part of the GI tract in addition to systemic inflammatory presentations. According to the affected area of the GI tract and its manifestations, the disease is called Crohn's Disease (CD) or Ulcerative Colitis (UC). Increase in the incidence of IBD as well as lack of cure bring IBD into special considerations. Several evidences in the recent years support involvement of genetic predisposition, environmental factors, microbial infection and immune dysregulation in pathophysiology of IBD.

One of the main areas of investigation is the role of oxidative stress in IBD that is believed a potential etiological and/or triggering factor (Rezaie *et al.*, 2007b). It was shown that the salivary level of transforming growth factor $\beta 1$ (TGF- $\beta 1$), lipid peroxidation (LPO) and Nitric Oxide (NO) in CD patients is higher than healthy subjects while the level of Total Antioxidant Capacity (TAC), albumin and uric acid is lower. Also, CD activity index (CDAI) was significantly correlated with TAC and LPO (Rezaie *et al.*, 2006). In an investigation excessive NO production in saliva of CD and UC patients was shown while only saliva of CD patients was oxidatively stressed and salivary Epidermal Growth Factor (EGF) level were significantly higher in CD patients (Jahanshahi *et al.*, 2004). Although, the abnormal amount of NO and TGF- β was found in saliva of UC patients, their DAI was not correlated with those mediators (Rezaie *et al.*, 2007a). Increased levels of TGF- $\beta 1$, NO and LPO in the saliva of CD patients underlines the importance of oxidative stress in its pathogenesis (Rezaie *et al.*, 2006).

Parallel with other investigations, the efficacy of nicorandil at low doses in animal colitis was observed by reducing macroscopic and histological damages suggesting the mechanisms as NO donation and free-radical scavenging properties (Hosseini-Tabatabaei and Abdollahi, 2008; Hosseini-Tabatabaei *et al.*, 2009). According to this, drugs with anti-inflammatory and antioxidant properties may alleviate DAI and induce or maintain remission. In another study, N-acetyl cysteine (NAC) by its anti-inflammatory properties at moderate to high doses improved cellular biomarkers of IBD in mice (Ebrahimi *et al.*, 2008). Also, the protective effect of silymarin on bowel cells through antioxidant and anti-inflammatory properties was revealed (Esmaily *et al.*, 2009). Supporting hypothesis of oxidative stress, combination of silymarin and nano-selenium was found useful in experimental colitis through inhibition of nuclear factor κB (NF- κB) (Miroliaee *et al.*, 2011).

Several clinical trials have examined the efficacy of anti-tumor necrosis factors on CD. A meta-analysis in 2007 revealed that anti-tumor necrosis factors including infliximab, cetrolizumab, CDP870, CDP571, etanercept and onarcept improve clinical response in 2 weeks but the effect after 2 weeks is not significant (Rahimi *et al.*, 2007a). Infliximab as an anti-TNF agent was found more effective than corticosteroids in inducing remission in UC but it caused more side effects (Rahimi *et al.*, 2007b; Nikfar *et al.*, 2011). Other than anti-TNF agents, 5-aminosalicylates can induce and maintain remission in mild-to-moderate colitis (Rahimi *et al.*, 2009b; Nikfar *et al.*, 2009).

Fistula is a common complication of CD and occurs in 20-40% of CD patients which is resistant to conventional therapy. Attention to the role of special cytokines such as EGF and NO brings biologic therapies into special consideration of which infliximab can induce remission in fistulizing CD (Rezaie *et al.*, 2005). Nikfar *et al.* (2010b) meta-analyzed nine clinical trial in immunoregulators and two in antibiotics in the efficacy and tolerability of these two groups of drugs in fistulizing CD. They demonstrated efficacy of immunoregulators and antibiotics in 50% reduction of the number of open active draining fistulas as well as fistula closure while their safety was similar.

The benefit of antibiotic therapy on pouchitis was confirmed in a systematic review including a meta-analysis (Elahi *et al.*, 2009). In another meta-analysis significant effect of antibiotics in preventing pouchitis after restorative Ileal Pouch Anal Anastomosis (IPAA) was revealed (Elahi *et al.*, 2008) and more significant results were obtained after pouchitis (Nikfar *et al.*, 2010a). In addition, antibiotics showed efficient as adjunctive therapy for induction of clinical remission in UC in meta-analysis (Rahimi *et al.*, 2007c).

Phosphodiesterase (PDE) enzyme especially PDE4 exists in the most inflammatory and immunomodulatory cells and its inhibition may affect several inflammatory diseases. In this regard, tetomilast-a second generation PDE 4 inhibitor

(PDI4)-showed favorable effects in phase II studies with acceptable safety profile in IBD (Salari-Sharif and Abdollahi, 2010). Furthermore the potential antioxidant properties of sildenafil (phosphodiesterase 5 inhibitor) were also determined (Khoshakhlagh *et al.*, 2007).

The safety profile of standard therapies and their low efficacy led to emergence and implication of complementary and alternative medicine in different forms including herbal therapies and probiotics in IBD. Literature review shows promising efficacy and good safety profile of herbal therapies by different mechanisms such as immune system regulation, antioxidant and anti-platelet activities (Rahimi *et al.*, 2009a). Naturally derived antioxidants are other therapies which are under investigation. In an attempt into getting more information about their safety and efficacy, IMOD was compared with dexamethasone and infliximab in experimental colitis on rats and significant reduction in macroscopic and histologic damage scores was observed (Baghaei *et al.*, 2010). In addition the benefits of essential oil from *Satureja Khuzestanica* Jamzad (SKEO) showed comparable effects to that of prednisolone (Ghazanfari *et al.*, 2006). The anti-inflammatory and antioxidant properties of *Teucrium* was demonstrated through reducing the cellular concentration of TNF- α , IL-1 β , etc. in rat colitis (Abdolghaffari *et al.*, 2010). Theoretically Iranian traditional medicine can affect IBD through anti-inflammatory, antioxidant and immunomodulatory properties (Rahimi *et al.*, 2010).

Recently probiotics have been studied as useful agents in maintaining remission of CD. A meta-analysis on 8 clinical trials failed to demonstrate the efficacy of probiotics in maintaining remission in CD (Rahimi *et al.*, 2008a) however, their effect in maintaining remission in UC was comparable with mesalazine (Rahimi *et al.*, 2008b).

Taken together, the present evidences suggest revisiting therapeutic guidelines especially in patients experiencing preliminary states of IBD.

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