COMPLEMENTARY IBD THERAPIES; WHAT TO RECOMMEND?

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1. VITAMIN D
2. CURCUMIN
3. DIET
4. FMT

Connection to IBD
WHY DO WE CARE?

Search for other options
Patients are asking and investigating

Anti-TNF Therapy for Maintenance of Remission/Complete Response

**Luminal CD**
- Week 54

- Placebo (N=110): 14%
- Infliximab 5 mg/kg (N=113): 28%
- Infliximab 5-10 mg/kg (N=112): 38%

**Fistulizing CD**
- Week 54

- Placebo (N=98): 23%
- Infliximab (N=91): 46%

*Clinical Remission: CDAI ≤ 150

*Complete Response: Absence of draining fistulae

CROHN’S SURGERY

50% require surgery in 10 years
Clinical manifestations of a dysregulated, uncontrolled immune response to an exogenous luminal antigen in a genetically susceptible host
Vitamin D – It’s not just the bones
VITAMIN D

Nonclassical roles
EPIDEMIOLOGIC ASSOCIATION OF VITAMIN D AND IBD

North – South Gradient
Barrier Function
Production of defensins/cathelicidin

DEFENSIN FUNCTIONS
(1) Defend from pathogens
(2) Shape microbiota
(3) Protect stem cells

PCs

Peyer’s patch

- Defensins
- Bacteria
EFFECTS OF 1,25D3 ON CELL TYPES OF IMMUNE SYSTEM

Macrophages

- Reduce MHC2. Decrease IL-6 and IL-23. Decrease TNF-α and IL-1. Increase cathelicidin, phagocytosis, and chemotaxis. Stimulate antimicrobial response. Upregulate VDR, CYP27B1, and CYP24A1.
EFFECTS OF 1,25 D3 ON INNATE CELLS

Dendritic

- Impede T-cell/DCs interaction.
  - Decrease IL-1, IL-2, TNF-α, and INF-γ.
  - Increase IL-10 and TGF-β.
  - Diminish T cell activation.
  - Inhibit differentiation, maturation, activation, and survival.
  - Decrease MHC2 (CD40, CD80, and CD86).
  - Reduce IL-12.
  - Up regulate ILT3 and ILT4.
  - Inhibit Th1 response indirectly.
  - Inhibit Th17 cell induction.
  - Affect chemokine production (increase CCL2, CCL18, and CCL22, and decrease CCL17 and CCL20).
  - Increase maturation-induced apoptosis.
1,25 D3 EFFECTS ON IMMUNE CELLS

T cells: CD4+
T cells: CD8+
T cells: Treg
T cells: γδ T
T cells: memory T cells: NK

- Inhibit proliferation.
- Inhibit INF-γ.
- Increase IL-4, IL-5, and IL-10.
- Decrease IL-17, IL-6, and IL-23.
- Inhibit Th17 activity.
- Express high level of VDR.
- Express 1α-hydroxylase.
- Reduce INF-γ and TNF-α.
- Increase IL-5 and TGF-β.
- Promote induction.
- Inhibit expansion.
- Inhibit INF-γ production.
- Downregulate CD25.
- Potentiate cell death.
- Suppress IL-17A, IL-17F, TNF-α, and IL-22. Attenuate NK activity.
- Stimulate NK activity.
1,25 D3 ON IMMUNE CELLS

B cells

- Inhibit proliferation.
- Upregulate p27 gene.
- Inhibit plasma cell generation.
- Inhibit memory B cell generation.
- Inhibit IgG and IgM secretion.
- Induce apoptosis.
- Induce CYP27B1, CYP24A1, VDR, and TRPV6.
- Induce IL-10 and CCR10.
Figure 2 Immunomodulatory actions of vitamin D
Mouse Models

- Vitamin D deficiency exacerbates ileocolitis in IL-10 knockout mice, but supplementation with Vit. D reduces inflammation and improves histologic scores.

VITAMIN D AND IBD

Seasonal variations

- Ananthakrishnan. Review article: Vitamin D and inflammatory bowel diseases Alimen. Pharm. & Ther. 2014 January- Higher prevalence of Vitamin D deficiency in IBD patients, Low Vitamin D levels are more likely to have IBD-related surgery and hospitalizations.
VITAMIN D AND IBD

Relapse rate

- Jorgensen SP et al. *Aliment Pharmacol Ther.* 2010 May 11. Relapse rates are lower in CD patients with normalization of Vitamin D level
VITAMIN D

Sustainability of treatment

VITAMIN D

Sustainability of treatment

- Reich KM et al. *Inflammatory Bowel Dis. J.* Jan. 2016 Role of Vitamin D in Infliximab-induced Remission in Adult Patients with Crohn’s Disease
Vitamin D study issues

- Need larger studies
- No agreement on serum level that produces immunomodulation
Turmeric and/or curcumin

- Asian spice used for centuries as a natural therapy for skin and intestinal disorders
- Curcumin 1 gram BID
- Anti inflammatory effects: decreases NF-KB
- Immunosuppressant properties by inhibition of TNF-alpha and IL-2
Oxygen derived Free Radicals

Types: Endogenous and Exogenous Free Radicals

Formation of Free Radicals

- UV Light
- Ionizing Radiation
- Smoking
- Metabolism
- Inflammation
- Air Pollution
- Ozone + UV (in air)
- UV
Oxygen Derived Free Radical

A missing electron creates a “Free Radical”, highly reactive.
ROS and Immune system

- Lowers the threshold for activation of T cells
- Directly stimulates the protein (NFKB) that stimulates transcription of cytokines
Excess Oxygen Free Radicals

- Cell damage
- Unregulated immune activation
- Exposure of immune system to luminal antigens
- Several studies have documented high NO levels in IBD
Curcumin Add-on Therapy for Remission Induction in Mild-moderate Active Ulcerative Colitis: A Multi-center, Randomized, Placebo-Controlled Trial
