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REVIEW

Why interleukin-10 supplementation does not work in Crohn's disease patients

Gareth J Marlow, Dominique van Gent, Lynnette R Ferguson

Gareth J Marlow, Dominique van Gent, Lynnette R Ferguson, Discipline of Nutrition, Faculty of Medical and Health Sciences, The University of Auckland, Auckland 1142, New Zealand
Gareth J Marlow, Lynnette R Ferguson, Nutrigenomics New Zealand, The University of Auckland, Auckland 1142, New Zealand
Author contributions: All authors contributed equally to this paper.
Supported by The Ministry of Business, Innovation and Employment; Dutch Digestive Foundation
Correspondence to: Lynnette R Ferguson, Professor, Discipline of Nutrition, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. l.ferguson@auckland.ac.nz
Telephone: +64-9-9236372 Fax: +64-9-3035962
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Abstract

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) or ulcerative colitis are chronic intestinal disorders, which are on the increase in "Westernised" countries. IBD can be caused by both genetic and environmental factors. Interleukin-10 (IL-10) is an immunoregulatory cytokine that has been identified as being involved in several diseases including IBD. Studies have shown that polymorphisms in the promoter region reduce serum levels of IL-10 and this reduction has been associated with some forms of IBD. Mouse models have shown promising results with IL-10 supplementation, as such IL-10 supplementation has been touted as being a possible alternative treatment for CD in humans. Clinical trials have shown that recombinant human IL-10 is safe and well tolerated up to a dose of 8 μg/kg. However, to date, the results of the clinical trials have been disappointing. Although CD activity was reduced as measured by the CD activity index, IL-10 supplementation did not result in significantly reduced remission rates or clinical improvements when compared to placebo. This review discusses why IL-10 supplementation is not effective in CD patients currently and what can be addressed to potentially make IL-10 supplementation a more viable treatment option in the future. Based on the current research we conclude that IL-10 supplementation is not a one size fits all treatment and if the correct population of patients is chosen then IL-10 supplementation could be of benefit.

Key words: Inflammatory bowel disease; Crohn's disease; Interleukin-10; Recombinant human interleukin-10

Core tip: Inflammatory bowel disease (IBD) is a chronic condition with no known cure. This review addresses the current available treatments for IBD before discussing a potential new treatment strategy using the immunoregulatory cytokine interleukin-10 (IL-10). To date clinical trial results have been disappointing. We highlight the limitations of current IL-10 supplementation treatment and suggest how, with changes to IL-10 delivery and the correct choice of patient, IL-10 supplementation could become a viable treatment option.

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INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic intestinal disorders that are typified by ulcerative colitis (UC) and Crohn's disease (CD). They are considered to be caused by an aberrant intestinal immune response to commensal microbiota in genetically susceptible individuals[1-3]. IBD

affects over 1.4 million people in the United States and over 2.2 million in Europe and is on the increase[4-7]. In New Zealand CD affects 16 per 100000 and UC 7 per 100000. Clinical symptoms include pain, diarrhoea, rectal bleeding and weight loss, which can have a debilitating effect on sufferers[8]. There are both environmental and genetic factors that have a role in the development and progression of IBD. IBD is more prevalent in "Westernised" countries, believed to be a result of diet and lifestyle and also an effect of improved sanitation[9-11].

Genome-wide association studies (GWAS) have highlighted the complexity of IBD. To date, 163 IBD susceptibility loci have been identified[12], 30 associated with CD, 23 with UC and 110 with both[10,12-14]. Some susceptibility genes have been identified, covering genes involved in autophagy (*ATG16L1* and *IRGM*), pattern recognition receptors, intestinal epithelium maintenance and immune response[4].

The anti-inflammatory cytokine interleukin-10 (IL-10) has been identified as being involved in IBD[15]. Studies[16-18] have shown that polymorphisms in the *IL-10* promoter alter IL-10 serum levels and have been linked to IBD. IL-10 supplementation has been tested as a potential therapy for CD[19-28]. This review will focus on the use of IL-10 supplementation explaining why it is currently ineffective at treating patients with CD and showing how that effectiveness could be improved.

IL-10

Functions of IL-10

IL-10 was first identified as a cytokine secreted by $CD4^+$ Th2-cells that inhibits cytokine production in antigen presenting cells[29], and was described as a cytokine synthesis inhibitory factor. The gene for human *IL-10* is located in the 1q32 band on chromosome 1 and encodes for 5 exons. The encoded protein is a homodimer with a mass of 37 kDa consisting of 160 amino acid monomers[16,19,30]. The structure of IL-10 resembles interferon gamma (IFN-γ) and both IL-10 receptor (IL-10R) subunits are members of the interferon receptor family[31,32].

IL-10 is a pluripotent cytokine and could be considered the most important anti-inflammatory cytokine found in the human immune response[4,19]. IL-10 is produced by different cell types including B- and T-lymphocytes, macrophages, monocytes, dendritic cells and mast cells[16,33]. IL-10 has the ability to differentially affect the function of different subsets of immune cells, affecting both the innate immune system and the adaptive immune system, and is therefore considered to have a broad effect in immunoregulation and host defense[34]. Broadly speaking, IL-10 inhibits pro-inflammatory mediator production while increasing the production of anti-inflammatory mediators[19,34].

Many of the pro-inflammatory cytokines suppressed by IL-10 are known to be regulated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Dysregulation of NF-κB has been implicated in the pathogenesis of chronic inflammatory disease including IBD[35,36]. It has been shown that IL-10 can block IKK activation and directly inhibit the nuclear localisation ofthe NF-κB p65/p50 heterodimer[37,38]. It has also been shown that IL-10 can selectively induce nuclear translocation and DNA-binding of p50 homodimer, which has been shown to inhibit transcription[39].

IL-10 down-regulates major histocompatibility complex Ⅱ (MHC class Ⅱ) expression[40] and the expression of the co-stimulatory ligands CD80/CD86 (B7-1, B7-2) in monocytes[41], macrophages[42,43] and dendritic cells[44,45]. While both MHC class Ⅱ and co-stimulatory ligands are needed to effectively activate $CD4^+$ Th2 cells by antigen presentation, this results in decreased macrophage and T cell derived cytokine synthesis, *e.g.*, IL-1, IL-6, IL-8, IFN-α, tumor necrosis factor-α[25,46-48]. However IL-10 also has immunostimulatory effects, by up-regulating MHC class Ⅱ expression on B lymphocytes[49] and increasing the synthesis of several antibody isotypes *e.g.,* immunoglobulins (IgM, IgA and IgG)[50].

Despite unanswered questions, our current knowledge credits IL-10 with having a significant critical role in regulating intestinal immune homeostasis, this is highlighted by the fact that impaired IL-10 signalling contributes to IBD[4,51,52]. Rare homozygous mutations in *IL10RA* and *IL10RB*, resulting in defective IL-10 signalling were identified in children with early-onset IBD[52] thereby confirming IL-10's critical role in maintaining intestinal homeostasis.

IL-10 signalling

During IL-10 signalling the IL-10 homodimer binds to the tetrameric receptor IL-10R complex, consisting of 2 molecules of IL-10R α-chain (IL-10R1) and two molecules of the IL-10R β-chain (IL-10R2)[53-55]. This binding activates Janus Kinase 1 (JAK1) and tyrosine kinase 2 (Tyk2), which self-phosphorylate and subsequently phosphorylate IL-10R1 at tyrosine residues, 446 and 496, which recruits signal transducer and activator of transcription 3 (STAT3) *via* its SH2-domain. STAT3 is phosphorylated by JAK1 and Tyk2, causing dimerisation and translocation to the nucleus, where target genes are induced[2,4,20,53] (Figure 1).

There is contradictory evidence regarding the role of STAT3 in IBD[56], with studies showing that it can play both a pathogenic[57-60] or a regulatory[61-64] role in IBD depending on the specific activator and cell type[65]. STAT3 mediates mucosa-protective functions in epithelial and myeloid cells but can also contribute to inflammation if active in other cell types[66]. It has been shown that STAT3 is essential for all known functions of IL-10 and that STAT3 acts as a transcription factor for other genes within the anti-inflammatory response[67,68]. STAT3 is primarily recruited and activated in macrophages, and this activation is transient[69], which avoids the inflammation associated with an increase of activated STAT3 in IBD[70-72].

Genetic variants in *IL-10*, the IL-10 receptor and *STAT3* genes are associated with IBD, highlighting the

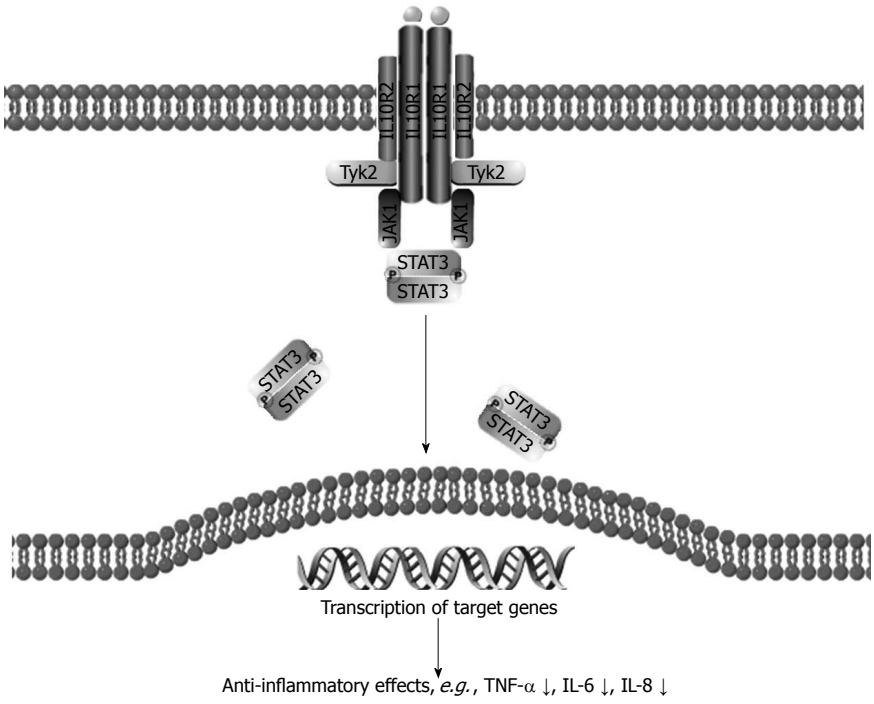

Figure 1 Interleukin-10 signalling pathway. Interleukin-10 (IL-10) binds to the tetrameric receptor IL-10 receptor (IL-10R) complex, this activates Janus kinase 1 (JAK1) and tyrosine kinase 2 (Tyk2), which self-phosphorylate resulting in the binding and phosphorylation of signal transducer and activator of transcription 3 (STAT3). STAT3 dimerises and translocates to the nucleus, inducing target genes. TNF-α: Tumor necrosis factor-α.

involvement of the IL-10 signalling cascade in the pathogenesis of CD and UC, further supporting the hypothesis that defective anti-inflammatory mechanisms may be key to IBD development[2,11,15,52,73-75].

IL-10 AND IBD

How IL-10 relates to IBD

The first evidence of a role of IL-10 in IBD, came from a GWAS study by Franke *et al*[15] that showed a significant ($P = 1.35 \times 10^{-12}$) association between a single nucleotide polymorphism (SNP) rs3024505 near the three-prime untranslated regions of the *IL-10* gene and UC, there was modest association with CD.

IL-10 knockout mice develop chronic enterocolitis, which is similar to human CD, if they are not kept in germ-free conditions. Administration of IL-10 ameliorates inflammation in both animal and *in vitro* models[76], indicating a potential role for IL-10 in the down-regulation of Th1-mediated mucosal inflammation[16,77].

Because IL-10 mediated immune responses are so important in maintaining intestinal homeostasis and commensal flora tolerance, it has been hypothesized that a defect in IL-10 production may be involved in the pathogenesis of CD[78]. In fact impaired IL-10 production has been found in severe cases of both UC[79] and CD[78]. Studies show that CD patients have normal[80,81] or high IL-10 levels[18,82]. However, low IL-10 production in intestinal mucosa has been shown to be associated with increased postoperative recurrence[22,83] and it has been shown that administration of recombinant human IL-10 in low IL-10 producers significantly reduced recurrence after surgery[22].

IL-10 mucosal levels

It has been shown that intestinal epithelial cells from healthy and inflamed colonic tissue express IL-10 mRNA and protein to the same extent. However during inflammation and also in patients with CD, there are significantly increased numbers of mononuclear cells producing IL-10[20,25]. Circulating levels of IL-10, as determined by serum levels of IL-10[82] and mRNA levels[84], have been shown to correlate with disease activity.

IL-10 serum levels

It is believed that circulating levels of IL-10 are critical in immune regulation. Basal levels of IL-10 modulate production of other cytokines and thus minor changes can affect the cytokine network, which in turn affects inflammation.

Studies have been inconsistent regarding serum levels of IL-10 in IBD, as stated earlier some studies show higher IL-10 levels in CD, Wang *et al*[18] found that CD patients had significantly higher levels of IL-10 compared to controls. Kucharzik *et al*[82] reported increased serum IL-10 concentrations in patients with active CD or UC compared to controls. Mitsuyama *et al*[85] showed an increase in serum IL-10 in active UC patients but not CD. In contrast, Nielsen *et al*[81] reported that serum IL-10 concentrations did not differ among UC, CD and healthy control subjects. These inconsistencies could be the result of variations, *e.g.*, age, severity of disease and ethnicity in the studied populations or in different methodological designs.

As IL-10 is an anti-inflammatory cytokine, we expect that high serum levels of IL-10 are likely to be good for patients with chronic inflammatory disease. In fact low IL-10 levels are known to increase disease severity in CD patients compared to high IL-10 levels[85,86]. From steroid treatment it has been shown that steroid non-responders have low IL-10 levels while steroid responders have sus-

tainable high IL-10 levels during and after treatment[87]. Sufficient IL-10 levels seem to be required for recovery but do not offer a cure.

We can hypothesize that IL-10 has an optimal level to be beneficial to reduce chronic inflammatory diseases, and may prove detrimental at too high or too low levels. Diseases associated with IL-10 SNPs such as psoriasis and rheumatoid arthritis are known to have high IL-10 serum levels[18,88,89], while in other diseases like UC, IL-10 levels vary between individuals and studies, with a trend toward increased IL-10 production, though the big studies are lacking[90-92].

IL-10 serum level and disease severity is not restricted to IBD, other diseases including autoimmune diseases, such as systemic lupus erythematosis, Behçets, type 1 diabetes mellitus[14], psoriasis[93], atherosclerosis[94] and rheumatoid arthritis[89] have all been shown to be associated with *IL-10* SNPs. Susceptibility to several cancers including prostate[95], breast[96], cervical[97] and more recently gastric[98,99] have been associated with *IL-10* promoter polymorphisms.

IL-10 promoter polymorphisms

SNPs are the most common form of genetic variation in humans. A SNP occurs at a location where more than one possible nucleotide occurs naturally within a population at a frequency >1%[100]. SNPs can be in both coding and non-coding regions of DNA. Due to the degeneracy of the genetic code. Even if the SNP is in a gene it may not change the amino acid and so has no effect on the protein (synonymous SNP), however non-synonymous SNPs do change the protein and are more commonly associated with disease. It is these variations that are most interesting to researchers as these can account for whether/how a person develops a disease, the severity of disease and how they respond to treatment.

Important variability in IL-10 secretion has been reported and is associated with SNPs in the *IL-10* promoter at 3 locations -592, -819, -1082[78,101,102]. The *IL-10* promoter polymorphisms C-592A (rs1800872), C-819T (rs1800871) and G-1082A (rs1800896) have been extensively studied. The most recent studies of Franke *et al*[15], Amre *et al*[17], Wang *et al*[18], Andersen *et al*[73], Fowler *et al*[103], Fernandez *et al*[104] and Tedde *et al*[105] reported a significant association between IL-10 rs1800896 and IBD.

The "A" allele of rs1800896 was found to be more common in IBD patients, especially in UC patients, individuals with the A/A genotype have lower IL-10 production than the G/G genotype[106], Koss *et al*[107] found that the -1082 AA is associated with decreased IL-10 production in both CD patients and controls. Wildtype -1082 (rs1800896) "G" and -592 (rs1800872) "C" are known to be associated with increased IL-10 levels; therefore we expect the GCC haplotype to show the highest IL-10 expression and ATA the lowest. This hypothesis was studied by Reuss *et al*[108] who showed in THP-1 monocyte cells that IL-10 expression was highest in the GCC haplotype compared to ACC and ATA (P = 0.042 and P = 0.0026). In the twin-study which followed, the haplotype showed no correlation with IL-10 serum levels. Wang *et al*[18] showed a significant (P = 0.001) increase in IL-10 production for TAT haplotype in healthy controls. The -592A allele was also shown to be associated with reduced transcription and decreased IL-10 secretion[16,102,109].

CURRENT IBD TREATMENTS

The current treatment options available for IBD, include: surgery, aminosalicylates, *e.g.,* 5-aminosalicylic acid, corticosteroids, *e.g.,* prednisone, immunosuppressants, *e.g.,* azathioprine, cyclosporine or biologicals, *e.g.,* infliximab[110,111]. The choice of treatment is dependent on phenotype, disease activity, characteristics of the drug and the patient. The choice should look to balance effectiveness with side effects and long term complications. As with any drug treatment there are side effects, these range from the usually well-tolerated upset stomach, nausea and headache to the more severe bone marrow and liver problems. As well as the associated side effects these treatments only work for some cases and can also result in a loss of response. Thus stronger treatments are required which have more severe side effects and long term consequences, and so alternative therapies are being investigated.

ALTERNATIVE TREATMENTS

Environmental and dietary factors are thought to play a role in the development of CD[112,113] and so changes to diet and lifestyle can have beneficial effects. Studies[114-118] have shown that specific foods are associated with IBD and that avoiding certain foods can reduce both the severity and frequency of symptoms. There are several classes of new drugs being developed: monoclonal antibodies, small molecules, fusion proteins and recombinant growth factors, as well as stem cell based therapies; one of these new therapies is IL-10 supplementation.

IL-10 supplementation for CD

Studies have suggested that IL-10 has huge therapeutic potential in intestinal inflammation, and that it should inhibit the up-regulated pro-inflammatory cytokines in CD and UC[25]. In most studies to date, Tenovil (Schering-Plough, Kenilworth, NJ, United States), has been used, which is the brand name of rhuIL-10. It is produced by a genetically engineered *Escherichia coli* strain, that expresses a 161 amino acid protein identical to human IL-10 with an additional amino-terminal methionine residue[119,120].

Why doesn't it work?

Based on the success of animal models[121-126] of intestinal inflammation, IL-10 therapy was heralded as a potential anti-inflammatory treatment in CD and several human trials have been undertaken. The first trial conducted by van Deventer *et al*[28] showed that IL-10 supplementation

Table 1 Summary of key findings from interleukin-10 trials in human and animal studies

Ref.	Model	Intervention	Outcome
	Human		
Colombel *et al*[22]	65 patients having recently undergone intestinal resection surgery	4 μg/kg daily or 8 μg/kg twice weekly for 12 wk	No clear evidence of effect
Fedorak *et al*[23]	95 mild to moderately active CD (CDAI 200-350)	1, 5, 10 or 20 μg/kg of daily for 4, 20 wk follow up	Improved clinical response (based on CDAI score) and improved endoscopic appearance
Schreiber *et al*[26]	329 therapy-refractory chronic active CD (CDAI 200-400)	1, 4, 8 or 20 μg/kg of Tenovil subcutaneously for 28 d	Non-significant clinical improvements
van Deventer *et al*[28]	46 patients with active steroid-resistant CD (CDAI 200-350)	0.5, 1, 5, 10 or 25 μg/kg daily for 1, 3 wk follow up	Reduction in the average score of CDAI
Braat *et al*[128]	10 patients with moderate to severe CD	10 enteric-coated capsules containing 10^{10} cfu of LL-Thy12 twice daily for 7 d	Clinical benefit observed in 8 of 10 patients, including 5 showing complete remission
	Animal		
Barbara *et al*[121]	DNB induced colitis Spf Sprague-Dawley rats	Ad5IL-10 (5×10^8-1×10^{10} pfu)	Improved colitis macroscopically and histologically and decreased MPO activity and LTB4 levels
Grool *et al*[123]	40 male NZ white rabbits formalin-immune complex induced colitis	100 or 500 μg/kg single IV infusion of rIL-10	Anti-inflammatory response as measured by decreased mucosal damage, leukocyte recruitment, MPO and LTB4
Ribbons *et al*[124]	TNBS induced colitis in 74 Sprague-Dawley rats	0.5, 5, 50, 500 μg/kg rIL-10 subcutaneous injection twice daily for 5 d	Mild anti-inflammatory effects Significant reduction in MPO
Sasaki *et al*[125]	3% DSS induced C57B6 mice	Intra-peritoneal administration of adIL-10	Significantly reduced disease activity and weight loss and completely prevented histopathologic injury to the colon
Tomoyose *et al*[126]	4% DSS induced colitis BALB/c mice	Recombinant mouse rIL-10 (1, 100, 1000 unit/mL)	Marked improvement in intestinal inflammation Inhibition of tissue damage and production of pro-inflammatory cytokines
Steidler *et al*[127]	DSS induced and spontaneous IL10$^{-/-}$ mouse models of colitis	Daily intragastric inocula of 2×10^7 or 10^9 LL-mIL10	Reduced histological score by 50% in DSS and prevented onset of colitis in IL-10$^{-/-}$ mice

CD: Crohn's disease; CDAI: Crohn's disease activity index; cfu: Colony forming units; MPO: Myeloperoxidase; LTB4: Leukotriene B4; TNBS: 2, 4, 6 trinitrobenzenesulfonic acid; DSS: Dextran sodium sulphate; adIL-10: Adenoviral IL-10; DNB: Dinitrobenzene sulphonic acid; Spf: Specific pathogen free; Ad5IL-10: Human type 5 adenovirus + murine IL-10; pfu: Plaque forming units; LL-mIL10: *Lactococcus lactis* secreting murine IL-10.

was safe and well tolerated. This was confirmed by subsequent studies[22,23,26]. van Deventer *et al*[28] showed a reduction in the average score of CD activity index (CDAI), but this was not significant. Fedorak *et al*[23] showed that 5 μg/kg of Tenovil given subcutaneously for 28 d to patients with mild to moderate CD activity resulted in improved clinical response (based on CDAI score) and improved endoscopic appearance of the disease. Schreiber *et al*[26] showed that 8 μg/kg of Tenovil given subcutaneously for 28 d to patients with mild to moderate CD activity resulted in a non-significant clinical improvement. However, Colombel *et al*[22] found no evidence that treatment with Tenovil for 12 wk in CD patients after intestinal resection prevented recurrence of CD. The key findings of these studies are summarised in Table 1.

These data show that IL-10 treatment did not result in significantly reduced remission rates or clinical improvements when compared to placebo[21,24]. In fact a Cochrane review in 2010[21] concluded that "Interleukin 10 does not appear to provide any treatment of active Crohn's disease. ...interleukin 10 does not increase the number of remissions (complete or clinical), but increases the rate of withdrawal due to adverse events relative to placebo." This review only included three of the studies mentioned above[23,26,28] and although more patients receiving IL-10 withdrew from studies there was no significant difference in the number of patients reporting adverse reactions between treatment and control.

However this is not the whole story, as other studies not included in the Cochrane analysis have shown that patients respond differently to IL-10 supplementation. Colombel *et al*[22] reported that endoscopic recurrence in patients with low IL-10 levels at time of surgery reduced to 47% with Tenovil treatment compared to 80% in the placebo group. Schreiber *et al*[26] found that patients responded differently to IL-10 treatment, with patients suffering from high disease activity having a greater rate of clinical improvement. These data suggest that IL-10 levels and disease activity are factors in how a patient responds to IL-10 supplementation. Also, as previously stated, some CD patients already have raised levels of IL-10[18,82]. These patients will not benefit from IL-10 supplementation and may suffer detrimental effects as high doses of systemically administered IL-10 induce the pro-inflammatory cytokine IFN-γ[27].

The different response to IL-10 supplementation is not surprising given the heterogenous nature of CD. A therapy that targets one step within a complex immunological pathway may only benefit a small proportion of patients but if you select the correct sub-population of patients who under-produce IL-10, for example those that have a penetrating phenotype who have a greater deficiency in IL-10[78], you may see a significant beneficial response to IL-10 therapy[25].

There are five potential explanations as to why IL-10 treatment has not been effective as a therapeutic strategy: (1) the administered dose of IL-10 results in an intestinal concentration of IL-10 that is too low to elicit a response; (2) there are differences among individuals depending upon disease phenotype/severity; (3) IL-10 is only successful at preventing and not treating an established disease; (4) IL-10 alone fails to suppress all the pro-inflammatory mediators involved in chronic inflammation; or (5) IL-10's immunostimulatory effects counterbalance its immunosuppressive properties.

Can IL-10 supplementation work?

Most of the potential explanations as to why IL-10 supplementation currently doesn't work can be overcome.

The modest therapeutic benefits[23,26] and adverse effects can potentially be attributed to limited mucosal bioavailability of IL-10 and the fact that the trials so far have not separated patients by genotype or disease phenotype/severity. To address the low bioavailability of mucosal IL-10 without resorting to the detrimental high levels of IL-10 systemic administration, *Lactococcus lactis* (*L. lactis*) was engineered to secrete IL-10, and this was used to successfully prevent the onset of colitis in the IL-10 KO model and caused a 50% reduction in inflammation in the DSS mouse model[127]. This study was followed up with a small phase 1 human trial using *L. lactis* modified to contain the human IL-10 sequence (LL-Thy12)[128]. 10 capsules containing 1×10^{10} cfu of LL-Thy12 were given to 10 patients with moderate to severe CD twice daily for 7 d. The results showed this approach is both safe and biologically contained, avoiding the side effects associated with high systemic doses while still retaining the ability to reduce disease activity. This was a small trial in a controlled environment without a control comparison and so further studies are needed to confirm the effectiveness of this treatment. However based on these initial results this form of IL-10 supplementation is showing promise as a treatment for patients with chronic intestinal inflammation.

Alternative ways to improve local delivery of IL-10 include gene therapy using replication-deficient adenoviral vectors delivered directly to the gastrointestinal epithelial cells. This approach has proven successful in two mouse studies[121,129] showing an effect on colitis without the associated side-effects of systemic administration. Gelatine microspheres containing IL-10 (GM-IL-10) were developed by Nakase *et al*[130] to deliver sustained IL-10 release locally without losing bioactivity. Colonic inflammation in mice treated with GM-IL-10 was reduced compared to mice treated with IL-10 alone.

The second point of selecting patients based on disease phenotype and/or severity can be easily addressed based on clinical diagnosis. Selecting patients based on genotype is slightly more complicated and would require that potential candidates for treatment be screened. Genotyping has become relatively quick and easy to perform and the cost is reducing as the technology advances. However who actually performs the genotyping service, who pays for the service and gaining patient consent may be problematic. This could potentially be overcome by having the patients enrol onto a research study. However IL-10 serum levels are determined 50% by genetics and 50% by environment[108] and so just because a person has the low IL-10 producing SNP doesn't necessarily mean they will have low IL-10 levels. Therefore a better measure to determine potential benefit of IL-10 supplementation would be to measure the serum level of IL-10, which can be done using commercially available ELISA kits. This should prove to be easier to conduct and in gaining patient consent.

As mouse models proved[121,131] IL-10 administration was only successful when administered prior to initiation of colitis and was unable to treat any established inflammation. Therefore IL-10 supplementation could be used to prevent relapses rather than to treat active inflammation.

If locally delivered IL-10 fails to have an effect, then it may be due to the fact IL-10 alone is unable to suppress all the pro-inflammatory mediators involved in chronic inflammation.Therefore it would be necessary to develop a combination treatment containing IL-10. However the evidence suggests IL-10 alone should have an effect and so it may be that IL-10 supplementation is not a suitable treatment for that disease phenotype.

CONCLUSION

Based on this knowledge, it is our opinion that a subpopulation of CD patients, who have lower expression of IL-10, and who have active disease could benefit from targeted IL-10 supplementation therapy. However further studies are needed to determine the exact population of patients who would benefit the most from this treatment and to determine if there are any long term detrimental effects of this treatment. Given that current treatments of IBD may not be beneficial to a patient or have severe side effects, we believe it is worth exploring this potential treatment avenue.

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