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Sara Geraldes Pacheco Faria Paulino

Role of nutritional approach in the management of pediatric Crohn's Disease/ Valor da dieta nutricional na abordagem da Doença de Crohn pediátrica

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Role of nutritional approach in the management of pediatric Crohn's Disease

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Ao meu avô Pacheco

Role of nutritional approach in the management of pediatric Crohn's Disease

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ABSTRACT

Crohn's Disease is a chronic inflammatory condition whose incidence is increasing in children worldwide. Nutritional diet is now seen as a way to induce remission of pediatric Crohn's disease (CD) and is considered to be more secure than pharmacological therapies.

The aim of this review is to examine the role of enteral nutrition in the induction and/or maintenance of remission in pediatric CD and compare it to corticosteroid therapy. Novel diets enriched with omega-3 fatty acids, glutamine and transforming growth factor-beta (TGF-β) will also be addressed.

A search was performed based on *Pubmed*, *Scopus* and *Web of Science*. After screening titles, abstracts and some full texts, 44 articles were included.

Several studies proved that Exclusive Enteral Nutrition (EEN) is as effective in inducing clinical and biochemical remission of CD as corticosteroids. However, EEN is also capable of healing mucosa, improving height, weight and body mass index (BMI). Omega-3 supplemention has not been proven to be beneficial in the treatment of CD. Some trials investigated glutamine supplementation, but it was not demonstrated its superiority over standard diet. Besides achieving clinical and biochemical remission, TGF-β showed efficacy in mucosal healing and decreasing pro-inflammatory cytokine levels. Partial Enteral Nutrition (PEN) was not proved to be effective in inducing remission, but seems that it can be beneficial in the maintenance of remission.

Nutritional diet plays a crucial role in the management of pediatric CD, however some severe cases need pharmacological therapy which is not discussed in this review that concentrated on nutritional intervention.

KEYWORDS: Crohn's disease, treatment, nutritional diet, polymeric diet, pediatric, children

INTRODUCTION

Crohn's disease is a chronic inflammatory condition that can affect any part of the gastrointestinal tract. This disease can pop up at any age, mostly in the second decade of life. However incidence is increasing in children worldwide and up one quarter of the diagnoses are currently made during childhood (1).

This disease has a multifactorial etiology, as it depends on genetic, immunological and environmental factors. There is reasonable evidence that environmental triggers may affect intestinal mucous, microbiome and interaction with the mucosa and initiate an exacerbated adaptative immune response in genetically susceptible individuals, resulting in inflamation and luminal damage. It has been proven that diet is one of these environmental triggers (2-5).

In pediatric patients, nutritional deficiencies, due to reduced appetite and malabsortion, can lead to weight loss, malnutrition, growth failure (about 88% of patients), pubertal delay and impairment of disease recovery (1, 6). Furthermore, in pediatric-onset, CD tends to be more extensive and complicated compared to adults and as the genetic influence may have a more relevant role, leading to earlier clinical expression, this may be observed when there are more cases within the family (3, 7).

Pharmacological therapy continues to be the main option, including corticosteroids, immune modulators, biological agents and antibiotics. However, these agents entail relevant side effects, such as increased risk of infection or impairment of growth in children (3, 6).

Nutrition, besides being a source of energy, promotes linear growth and is now also seen as a secure way to induce remission of inflammatory bowel diseases. Nutritional diet as a therapy in CD was initiated in the beggining of the 1970's (8) and is currently considered to be the ideal treatment for pediatric patients (9). The mechanism of nutritional therapy in pediatric CD is still poorly known but there is some evidence that it may be due to bowel rest, modification of the of gut flora, enhancement of its barrier function, changes in antigenic stimuli and direct anti-inflammatory effect of the bowel (1).

The aim of this review is to examine the role of enteral nutrition in the induction and/or maintenance of remission in pediatric CD and compare it to corticosteroid therapy. Moreover, some novel diets enriched with anti-inflammatory nutrients such as omega-3 fatty acids and glutamine, as well as enriched with cytokines such as TGF-β will also be addressed as possible future ways to control the disease.

METHODS

A search was performed, in January 2017, based on the three databases: *Pubmed*, *Scopus* and *Web of Science*, using the following keywords (crohn's disease)AND(treatment)AND((nutritional diet)OR(polymeric diet))AND((pediatric)OR(children)). The search identified 151 articles on Pubmed, 173 on Scopus and 95 on Web of Science. Duplicated articles were excluded as those written in languages other than English. The results were not limited by size, date of publication or type of article. After reviewing the titles and abstracts, 75 articles were found to be of interest. Of these, those in which full text wasn´t available, were excluded. Full texts of the remaining articles were screened and were included those that showed relevant dietary evidence, focusing specifically Crohn´s disease. In the end, 44 articles were included in the review.

RESULTS

Enteral Nutrition – Induction of remission

Enteral nutrition has been a theme of discussion and research since its potential role in the treatment of inflammatory bowel diseases, back in the 70's was identified (8). The original diet consisted of elemental diet but subsequently it was observed that alternative options might provide some advantages. EEN is now considered to be the first line therapy to induce remission in children with active CD (7), consisting of a liquid diet as the only source of energy (10). Usually, EEN consists of simple components such as protein hydrolizates or amino acids, simple carbohydrates, fatty acids and vitamins (3).

Efficacy of EEN in pediatric patients has been proved by several studies (1, 10-13), resulting in induction of disease remission in a mean of 85% (14). Gavin *et al.* (15) examined data of 40 children newly diagnosed with CD, aged 6-16 years. After 8 weeks of exclusive feeding with a polymeric diet, all patients showed symptomatic improvement and weight gain. In 78%, C-Reactive Protein (CRP) serum levels decreased. The location of the affected intestinal segment did not significantly affect the results (small bowel, ileocolon and colon). Frivolt *et al.* (16) also analized health records of 52 children treated with EEN. Despite the fact that the majority of patients had moderate to severe disease activity, clinical remission rate at week 4 was 71% and the improvement rate was 25%. At week 12, remission rate had already been achieved by 92% of the children. One of the aims of this investigation was to compare results between the first and second courses of EEN. By the fourth week under EEN for the second time, 62% of the patients showed remission and 20% showed improvement. After one year, remission rate was 77%. Accordingly to this survey, EEN efficacy tends to decrease, reaching lower remission rates over the courses and

this may be influenced by genetic markers of disease susceptibility, namely NOD2. Guidelines of ECCO/ESPGHAN (7) define a standard period of induction therapy of 6 to 8 weeks and preferably using a polymeric formula rather than an elemental one, administered orally. Greater adherence to diet is achieved by oral administration comparing to nasogastric tube, that can be especially challenging for children and adolescents due to the changes in social dynamic around meals that make them frequently feel isolated from their peers. Yet, drinking the formula requires adequate motivation from the physician and patient to comply with therapy. Nasogastric tube may be used when oral intake is not appropriate and does not ensure delivery of all the required energy (10). Regarding type of formula polymeric diets are generally preferred due to better taste and lower cost. Elemental feeds should only be given in special conditions such as food allergies. Rodrigues *et al.* (17) evaluated a cohort of 45 children receiving polymeric formula and 53 receiving elemental formula; remission rates weren´t significantly different. Moreover, it was concluded that polymeric formula did not alter adherence to EEN, but significantly decreased change for nasogastric tube administration. Grogan *et al.* (18) also observed that rates of remission induction of these formulas were similar. However there was a small difference in plasma polyunsaturated fatty acids (PUFA) that may be important and needs further investigation. Polymeric formula increased eicosapentanoic acid (EPA) and alpha linolenic acid (ALA) and decreased arachidonic acid (AA), while elemental formula led to increase of EPA and AA and to decrease of docosahexaenoic acid (DHA). Another study that compared these two formulas (19) suggested that children under polymeric feed gained more weight, although rates of remission were not significantly different. As weight recovery is crucial in childhood and adolescence to ensure an adequate growth, polymeric formula seems to be superior to elemental.

EEN is capable, not only of inducing clinical and biochemical remission, but also to heal bowel mucosa, contrary to corticosteroids which cannot alter submucosal inflammatory processes (20, 21). Healing of mucosa influences long-term course of CD, representing a great advantage over corticosteroids. Besides correcting nutritional deficiencies, EEN positively affects height, weight and BMI, while corticosteroids can lead to growth retardation (14). In a prospective study (22), 34 children with a mean age of 13 years received EEN for 6 weeks and were followed to evaluate disease remission. After nutritional therapy, 84% reached clinical remission with 76% achieving both clinical and biochemical remission. Complete mucosal healing was obtained in 42% and in 21% there was complete transmural remission of small bowel. Berni Canani *et al.* (21) compared the effects between nutritional therapy and corticosteroids in patients with a mean age of 12 years. All of them improved their Pediatric Crohn's Disease Activity Index (PCDAI) scores after 8 weeks, independently of treatment. However endoscopic scores showed to be significantly better in children treated with diet and only this group achieved histological remission. A prospective controlled trial revealed similar results (20) in young patients with moderate to severe CD: in the fourth week of the trial, PCDAI, CRP, erythrocyte sedimentation rate (ESR) and serum albumin levels decreased equally in

both groups treated with polymeric feed and corticosteroids. There was increment in height, weight and BMI in both groups, but children under polymeric diet had a significantly higher weight gain (weight gain mean of 4.8 kg). Endoscopic and histological remission was only observed in polymeric diet group. Anti-inflammatory outcomes of polymeric formula were investigated in an *in vitro* model of epithelial cell inflammation, to better understand its mechanisms of action (23) in addition to the ability to change gut microflora. After several experiments, it was proposed that polymeric therapy has a direct effect on epithelial cells, causing reduction of interleukin-8 (IL-8) production. It was also suggested that some component of polymeric formulas inhibits phosphorylation of a cellular protein, IκBα, by proinflammatory stimuli, preventing NF-κB translocation to nucleus and consequent transcription of proinflammatory and immunoregulatory genes. This study confirmed a direct anti-inflammatory effect of polymeric diet on enterocytes, limiting production and release of chemokines in the presence of proinflammatory stimuli.

In terms of bone health, pediatric Crohn's disease causes disorganization of bone arquitecture, decreases bone mass and increases the risk of fracture (24). This is due to malnutrition, vitamin D deficit and use of corticosteroids (1). On the other hand, EEN appears to have an anabolic effect on the bone. In a group of newly diagnosed patients, an improvement of trabecular bone density and increase in cortical bone turnover was observed after treatment with EEN. This diet had already been associated with increased biomarkers of bone formation and reduced bone resorption in children. Furthermore, there seems to be improvement of muscle mass and increment in lean body mass as short-term effects (24).

Whilst induction of remission of CD can be achieved by EEN, maintenance of remission using the same strategy is more challenging given loss of adherence over time. However, children, treated with EEN for 8 weeks, who achieve remission have their risk of relapse decreased. Lambert *et al.* (25) studied the long-term outcomes of nutrition therapy and demonstrated a lower rate of relapse in the group under EEN comparing to children taking corticosteroids. Over 24 months of follow-up, 39% of patients treated with diet did not relapsed, while in corticosteroids group only 11% remianed stable. The mean of relapse episodes in EEN group was 0,5 (range 0-2) and 1,5 (0-8) in steroid group. Another survey investigated long-term outcome of gut microbiome after completion of EEN therapy (26). EEN changed bacterial composition of the bowel during the treatment, which may provide an anti-inflammatory effect. After completion of EEN period and return to normal diet, samples from the time of diagnosis and at 4 months post-therapy were compared and similarity of 40% in bacteria profile was observed. So, 4 months after nutritional induce of remission, intestinal microbiome partially reversed to initial bacteria profile, although not completely. The issue of the role of microbiome diversity in the pathogenesis and healing of CD is still under intense scrutinity. There is large consensus that decreased diversity is associated with higher risk of disease as compared to normal controls (27). However there is a paradoxical observation that

EEN while improving the disease and promoting mucosal healing also shows to induce lower microbiome diversity (28). But despite this paradox, there is some evidence that the sequential evaluation of the microbiome modification may predict the patients that will evolve into sustained remission after completing the treatment with EEN (27).

PEN therapy has also been considered to induce remission. This would mean treatment with a nutritional formula that ensures delivery of the majority of the energy required combined with limited amount of unristricted diet (10). Johnson *et al.* (29) studied 26 children under PEN and 24 under EEN and verified that remission rate of the first one was significantly lower (15% *vs*. 42% with EEN). Both groups had their PCDAI scores significantly diminished, but the decrease in EEN group was greater. Relatively to other disease indicators, PEN did not affect levels of haemoglobin, platelet count, CRP, ESR and albumin levels. In contrast, EEN showed improvement of haemoglobin and albumin levels as well as a significant decrease in platelet count and ESR. In conclusion, PEN is not effective in induction of remission of Crohn's disease.

Despite its clear benefit in most cases, regardless of intestinal location of the disease, EEN has not shown equal results in perianal disease where other medical and surgical options must be considered.

Several novel approaches for inducing remission have been examined and tested, such as enteral nutrition supplemented with omega-3 fatty acids, glutamine and TGF-β.

Omega-3 Fatty Acids

It is well established that diet high in fat, especially saturated fats of animal origin, has a proinflammatory efect. Regarding polyunsatured fats, omega-6 fatty acids (provided by corn oil, safflower seed and cottonseed for example) appear to be proinflammatory as well, while omega-3 fatty acids from fish oil or plant-based oils have anti-inflammatory activity. According to Lewis *et al*. (30), diet habits early in life may be important in determining predisposition for inflammatory bowel disease (IBD). There have been some studies trying to prove this association between early dietary patterns and the onset of CD. However it´s difficult to ensure that results are strong enough, because data are very heterogeneous and most of the surveys are retrospective studies based on dietary histories, hence have low accuracy owing to recall bias.

Nevertheless, some reviews suggest that an increased omega-6/omega-3 ratio is associated with higher risk of developing CD (14, 30, 31). A case-control study

(32) investigated the role of PUFA metabolic genes polymorphisms and dietary omega-6/omega-3 fatty acids ratio in the susceptibility of childhood-onset CD. This study showed that only children carrying particular CYP4F3 and FADS2 single-nucleotide polymorphisms have their risk increased. It was then proposed that these genotypes favor metabolism of n-6 PUFA and compromise metabolism of n-3, resulting in higher levels of proinflammatory mediators, when the fat intake ratio is high.

Although the replacement of n-6 for n-3 fatty acids can reduce the risk of CD, it seems that enrichment of enteral feeding with omega-3 fatty acids cannot induce remission or avoid the relapse of the disease. In fact, a Cochrane review by Lev-Tzion *et al.* (33) showed that omega-3 supplemention has not been proven to be beneficial in the maintenance or induction of remission of CD. On the other hand, a double-blind randomized multicenter trial (34) showed advantage in decreasing the amount of total fat and omega-6 fatty acids in enteral nutrition, concluding that type of dietary fat influences therapy. More investigation is needed to reach a valid conclusion towards the role of omega-3 supplementation in therapy of CD, but it is likely that there may be relevant influence of the genetic background into these specific benefits of fat manipulation.

Glutamine

Glutamine is a nonessencial amino acid that plays an important role in preserving the integrity of intestinal mucosa. In catabolic states, human body may demand amounts of glutamine that is unable to synthesize, resulting in glutamine deficiency, gut dysfunction and increased permeability (35). As CD leads to catabolic metabolism it has been suggested that glutamine may be defficent in active disease and that supplementation might be beneficial helping to improve bowel epithelial barrier (36). Indeed, there is evidence that children with CD have low plasma glutamine (35). However, experimental work did not confirm this benefit and, in fact, there may be some proinflammatory effect (31). A double-blind randomized controlled trial (36) investigated the effects of glutamine-supplemented enteral diet in 9 children and compared the results with those of another group of 9 children treated with standard diet. After 4 weeks of therapy, there were no significant differences in remission rates, platelet count, orosomucoid levels and weight. PCDAI scores of patients under standard diet were significantly lower than the scores of the other group. Thus, glutamine-enriched diet did not demonstrate superiority over standard diet in the treatment of pediatric CD. One possible explanation for this lack of benefit might be that glutamine also stimulates T-cells on the intestinal wall, resulting in inflammation, or that being a precursor of nitric oxid, it may promote mucosal damage.

Transforming Growth Factor-Beta

TGF-β is a cytokine with a very well recognized role in cell growth, cell differentiation and immunoregulation. As it controls differentiation, proliferation and activation of some immune system cells – macrophages, lymphocytes and denditric cells – TGF-β contributes to anti-inflammatory states and immune tolerance, softening autoimmune reactions (31). This effects can be extremely useful in CD treatment, making this peptide a potential new supplementation to enteral feeding as some studies have been proving.

A study compared fractionated oral *vs* continuous enteral feeding by nasogastric tube in children with moderate to severe disease activity (PCDAI > 30), using exclusively a specific oral polymeric diet enriched with TGF-β2 for 8 weeks (37). Remission was achieved in 75% of the children of oral group and 85% in the enteral group, but also promoted mucosal healing. In fact, all patients with mucosal healing showed clinical remission. Fell *et al.* (38) assessed clinical and endoscopic effects as well as mucosal proinflammatory cytokine mRNA in 29 pediatric patients treated for 8 weeks with a specific oral polymeric diet enriched with TGF-β2. Complete clinical remission was achieved by 79% of children. BMI and weight (mean of 3.2 kg) increased. Serum CRP and tumor necrosis factor α levels declined significantly. Mucosal macroscopic and histological improvement was observed, alongside with down regulation of mucosal proinflammatory cytokines. Thereby, it was possible to verify a fall of interferon ϒ mRNA levels in the ileum and a decreased level of IL-8 in the colon. Both ileum and colon demonstrated reduced levels of interlekin-1β mRNA. Finally, an increase of TGF-β1 mRNA in the ileum was found. The decline of these cytokine mRNA expression and concomitant clinical remission is consistent with the theory that CD activity is a consequence of an inflammatory bowel status (39). Of importance, one year after supplementation with TGF-β2, only 39% of the children relapsed, which is considerably lower than the relapse rate of enteral nutrition (65%) and corticosteroids (67%). Longer periods of administration are needed to appropriately evaluate efficiency of this protein in maintenance of remission (38). Hartman *et al.* (40) analized and compared disease activity of 28 Israeli children receiving TGF-β enriched formula to 18 children treated with standard polymeric formula and 18 children without supplementation. A significant decrease in PCDAI was noticed in the first two groups (from 34.3 to 15.7 and 35.0 to 22.0, respectively). No improvement was seen in the third group. Besides, only children receiving TGF-β registered significant improvements in ESR and BMI, which suggests a benefit of this type of formula in the treatment of pediatric patients with growth retardation.

Enteral Nutrition – Maintenance of remission

The use of EEN has gathered wide acceptance in the treatment of active CD in pediatric patients, although relapse occurs in a considerable number of patients in the following months (16). Maintenance of remission is therefore an important aspect of long-term treatment. To maintain remission for a longer period, various strategies have been evaluated involving nutritional manipulation. The use of PEN has also been considered in this context. A prospective study was conducted (6) to analize the effect of short-term suportive partial enteral nutrition (SPEN) in children with severe activity of disease. After one year of treatment, nutritional status indicators assessed by weight, height, hemoglobin, transferrin saturation, ferritin, albumin, some electrolytes and vitamins, changed siginificantly with SPEN. This improvement of nutritional status was more evident in the SPEN group constituted by younger patients (<13 years). Decrease of PCDAI score was also significantly higher in SPEN group than in non-SPEN one. This study has proved that SPEN as a secondary treatment along with conventional medical treatment is effective in improvement of nutritional status and in attenuating disease severity in children, especially in younger patients. Thereby, PEN is not effective in inducing remission, but it can be beneficial as a supportive therapy for maintenance of remission of pediatric CD. Clearly, the benefit of this approach requires long term motivation of the patient and family.

Another emerging type of therapy for maintenance of remisson that has been explored is exclusion diet.

Specific Carbohydrate Diet

Exclusion diets including selected and restricted ingredients, despite being very rigorous, if effective, may facilitate adherence by pediatric patients (11). Specific Carbohydrate Diet (SCD) is an attractive example of exclusion diet that may allow children to have a more normal life. This intervention removes refined sugars and restricts complex carbohydrates, since undigested and malabsorved carbohydrates lead to fermentation in the bowel, bacterial overgrowth and change fecal microbiome to a proinflammatory state (41). SCD restricts the intake of grains and starches such as wheat, rice, corn or potatoes. Alternatively, patients can eat baked food or breads made with nut, almond or coconut flours. Almost all milk products are eliminated, except for lactose free natural cheeses or fully fermented yogurt. Processed foods are prohibited and the only acceptable added sugar is honey. Recently, this dietary approach has been attracting interest as having therapeutic potential in IBD (42, 43). Several studies have demonstrated the efficacy of SCD in CD (2). Cohen *et al.* (43) examined clinical improvement, based on PCDAI, and mucosal healing in pediatric patients with active CD with a mean age of 13.6 years. After 12 weeks of SCD, 60%

of the patients showed clinical remission and 80% showed significant mucosal improvement, with 40% achieving mucosal healing. Suskind *et al.* (42) investigated medical records of routine clinic visits of 10 patients, aged between 7 and 16 years, within a regimen of SCD for 5-30 months. Laboratory parameters and fecal calprotectin significantly improved and in some patients even came to normal values. Regarding symptoms, after three months of treatment all of the patients had their symptoms solved. Seattle Children's Hospital IBD Center developed an integrated dietary program using SCD as primay therapy for IBD or as adjunctive therapy when there is partial response to medication (44). Medical records of a group of patients under SCD protocol were reviewed. Then, clinical and laboratory outcomes of this group and a control one were compared in certain periods of time (before diet, 2-6 week, 4-6 month, 7-11 month and in the 12th month of diet). There was an overal benefit in the disease activity but also some variation in the dietary protocol as well as weight loss in some cases due to inadequate compliance. This study suggests that there may be a role for dietary manipulation in the context of medical treatment but still insufficient to provide specific clinical guidance.

In terms of liberalization, Burgis *et al.* (41) performed a retrospective chart review of patients with CD treated with SCD. Patients were divided into two groups: one group included children treated with SCD alone or in combination with only antibiotics or 5-ASA, and the second group embraced children within SCD in combination with immunomodulators. After following a strict SCD, patients liberalized their own diet adding an illegal ingredient daily or adding illegal meals at varying frequency, sometimes daily as well. Hematocrit levels improved when children initiated strict SCD and remained stable with liberalization, in both groups. Albumin levels also significantly improved with strict diet, but a greater difference was noticed on SCD with immunomodulator group (0,9 g/dL *vs* 0.6 g/dL; *P*-value < 0.001). During liberalization time, albumin levels droped a little in this same group. There was significant decrease of ESR with strict diet that continued relatively stable with liberalized diet, without significant differences between groups. While on strict diet, most of the children improved weight (90%) and height (82%) percentiles. During liberalization period, it was observed just a small mean decline in weight (less than 1 percentile) and an increase in height percentile, resulting in a relatively stable growth. Therefore, it seems to be possible to adopt a less strict carbohydrate diet, carefully adding some ingredients and foods, and still remain in remission of CD.

However, the wide use of these approaches, especially if used without concomitant pharmacologic therapy requires careful previous validation. Dietary restrictions may induce nutritional deficiencies and indeed some of the patients have lost weight in some of the published studies. Furthermore, most cases of active pediatric CD occur in adolescents which is a delicate time for the growth spurt. Interference in this unique window for growth may limit the achievement of individual genetic potential. While it is desirable that research may provide clear

answers and recommendations regarding the use of nutrition as long-term tool to control CD, there must be great caution to avoid hasty advise that may turn to be deleterious in the long run.

CONCLUSION

EEN has shown to be the best option to induce remission in most cases of pediatric CD, leading to clinical, endoscopic and histological improvement, while correcting nutritional deficits ensuring linear growth of children. Due to similar efficacy, this nutritional approach compares favourably with corticosteroids, that bear some relevant side effects in children. Regarding supplemented diets, the role of enrichment with omega-3 fatty acids and glutamine is not conclusive, needing more investigation. TGF-β appears to be effective, leading to improvement of disease activity; therefore, it may enhance the overall benefit of EEN to induce remission. It is important to keep in mind that some cases with deep colonic ulceration, severe growth retardation and perianal disease may benefit from other concomitant or alternative pharmacological options that were beyond the scope of this review that concentrated on nutritional intervention. For maintenance of remission, PEN seems to be beneficial as a supportive therapy. Specific elimination diets, may prove to be of great benefit and clinical importance, as they may sustain clinical remission and mucosal healing while receiving improved compliance for long term treatment in pediatric patients and lead to some sparing of drug treatment.

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Anexos

Journal of Gastroenterology and Hepatology

Author Guidelines

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The Journal of Gastroenterology and Hepatology (JGH) is the official journal of the Asia Pacific Association for Gastroenterology. The Journal publishes peer-reviewed original papers, reviews, metaanalyses and systematic reviews, and editorials concerned with clinical practice and research in the fields of hepatology, gastroenterology and endoscopy. Papers cover the medical, surgical, radiological, pathological, biochemical, physiological, ethical and historical aspects of the subject areas. Clinical trials are afforded expedited publication if deemed suitable. JGH also deals with the basic sciences and experimental work, particularly that with a clear relevance to disease mechanisms and new therapies. Case reports and letters to the Editor will not be considered for publication.

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available at http://www.wma.net/en/30publications/10policies/b3/index.html. It should also state clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under the study should be omitted. Photographs need to be cropped sufficiently to prevent human subjects being recognized (or an eye bar should be used).

Registration of Clinical Trials

We strongly recommend, as a condition of consideration for publication, registration in a public trials registry. Trials register at or before the onset of patient enrolment. This policy applies to any clinical trial starting enrolment after July 1, 2008. For trials that began enrolment before this date, we request registration by December 1, 2008, before considering the trial for publication. We define a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase 1 trials) are exempt.

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(2) searchable by standard, electronic (Internet-based) methods;

(3) open to all prospective registrants free of charge or at minimal cost;

(4) validates registered information;

5) identifies trials with a unique number; and

(6) includes information on the investigator(s), research question or hypothesis, methodology, intervention and comparisons, eligibility criteria, primary and secondary outcomes measured, date of registration, anticipated or actual start date, anticipated or actual date of last follow-up, target number of subjects, status (anticipated, ongoing or closed) and funding source(s).

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Acknowledgments

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