MAINTENANCE INFILXIMAB TREATMENT FOR CROHN’S DISEASE OVER 54 WEEKS: OUR EXPERIENCE

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Background: The efficacy and safety of repeated infusions of Infliximab in the treatment of Crohn’s disease (CD) is recognized by international clinical trials (ACCENT I and II study) for a maintenance time of 54 weeks. Long-term Infliximab therapy results in a reduction of a rate of complications, hospitalizations and surgeries associated with CD. Literature data are not available for a longer period of time.

Aim: Our experience was conducted to monitoring the efficacy, safety and steroids tapering of patients affected by CD, already well responded to Infliximab, for more than 54 weeks.

Material and Methods: Twenty patients (pts), 11M, 9F, average 38 years (yrs), affected by CD with a long history of illness (median 9 yrs) were enclosed. All pts were parted into: fistulizing 9/20, refractory 8/20, stenosing 3/20 without indolent symptoms; 5/20 pts had previous surgical intestinal resections. Extraintestinal manifestations were arthralgia in 6/20, rheumatoid arthritis in 1/20, uveitis in 2/20 pts. Since the beginning of the treatment concomitant steroids were in every pts, Azathioprine (12/20), Tacrolimus (3/20), and MTX (11/20) only in few. All pts, already in treatment with Infliximab for more than 54 weeks and in remission CD (CAAI =< 150) were subjected to repeated infusions, every 8 wks, thereafter until 126 wks. At pre-defined study visits CDI, IBDQ, C-reactive protein values and steroid tapering were assessed.

Results: Five pts (25%) stopped the treatment for infusion reactions in 3/5 at the time of 66 and 106 wks and for surgical treatment in 2/5 fistulizing CD at 86 and 106 wks respectively. The other pts continued to the end of the study and showed from 56 to 126 wks a sustained clinical remission with CDI < 150 and IBDQ < 150 (p=0.012 and p=0.006 respectively); the C-reactive protein values decreased with significant results only at 126 wk (p=0.07). Moreover 14/20 (70%) pts were not receiving steroids at baseline continued without, the other 6pts (30%) with low dose of steroids didn’t get the withdraw, but kept periodically assuming.

Conclusions: Our preliminary experience explains a maintenance Infliximab treatment, safe and efficacy, for MC in remission for a time of 126 weeks. Only 40% of the pts interrupted the treatment before the end of the study. A longer time of Infliximab treatment didn’t increase the steroid tapering in those pts previously assuming. Further studies would be encouraged to better define the outcome of maintenance Infliximab treatment in pts with CD for a longer time.

TREATMENT OF ULCERATIVE COLITIS WITH A COMBINATION OF LACTOBACILLUS RHAHMOSUS AND LACTOBACILLUS ACIDOPHILUS. RESULTS OF A RANDOMISED, DOUBLE-BLIND, AND PLACEBO CONTROLLED TRIAL

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Introduction: In recent years, there has been an increasing interest in the relationship between the gastrointestinal flora and gut function. Several studies have shown promising results for the use of probiotics in the treatment of patients with inflammatory bowel disease.

Aims: Aim of the current study was to evaluate the effect of a probiotic containing Lactobacillus rhamnosus and Lactobacillus acidophilus for the induction and maintenance of remission in patients with active ulcerative colitis. The results were compared with a placebo group.

Methods: The study was a two-centre, randomised placebo-controlled, and double-blind trial. Patients above the age of 18 years with known ulcerative colitis with a clinical and endoscopic documented relapse could be included in the trial. Patients were randomised to treatment with a combination of Lactobacillus rhamnosus strain 19070-2 and Lactobacillus acidophilus strain 18911-2 (100E9 colony forming unit/ml) 1ml daily or an identical placebo. Patients were stratified according to whether or not they received systemic glucocorticoid treatment at inclusion. From inclusion and to remission patients were treated according to the physician’s standard guidelines and probiotics/placebo for 4-16 weeks. Patients achieving remission continued with maintenance treatment and probiotics/placebo for six months. Treatment with probiotics/placebo was stopped and patients were followed for either six months after this. The primary end-point was the number of patients without relapse (clinical and endoscopic documented) 6 months after remission had been achieved; secondary endpoint was the number of patients achieving remission.

Results: 102 patients (47 Males/55 Females) with a mean age of 38 years (range 21-75) were included in the trial. Fifty (49%) were randomised to treatment with probiotics, 52 (51%) to treatment with placebo. Sixtythree patients (62%), 35 treated with probiotics and 28 with placebo achieved remission, (p=0.07, n.s.). Six months after remission was achieved remission rate was no difference in the number of patients in remission in the probiotic and placebo treated group; 12 vs 13, (p= 0.47).

Conclusions: In a double-blind trial. Patients above the age of 18 years with known ulcerative colitis with a clinical and endoscopic documented relapse could be included in the trial. Patients were randomised to treatment with a combination of Lactobacillus rhamnosus strain 19070-2 and Lactobacillus acidophilus strain 18911-2 had no effect on the number of patients achieving remission or the number of patients in remission after 6 months.

RITUXIMAB AND ULCERATIVE COLITIS: AN UNEXPECTED BENEFICIAL COLLATERAL EFFECT OF LYMPHOMA TREATMENT

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The etiology of ulcerative colitis (UC) remains unknown, nevertheless there is good evidence that genetic, immunological and environmental factors play a determinit role in the development of the disease. Animal models of the disease and human data stress the role of a T cell-mediated pathology whereas the role of B cell-mediated pathology in UC remains controversiarial. Ruxitimab is a chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Its principal indication is the treatment of patients with Non-Hodgkin’s Lymphoma and Rheumatoid Arthritis. We report the case of a 33 year old female patient, known for a severe UC for 2 years that developed under methotrexate therapy a large immunoblastic B cell lymphoma whose treatment with ruxitimab was associated with a clinical remission of the UC. Methotrexate was introduced as treatment of her severe steroid resistant and ciclosporin independent UC after the failure of months of adequately-dosed azathioprine therapy. After 9 months of methotrexate therapy the patient, finally clinically in remission and ciclosporin as well as steroid-free, developed fever and peripheral lymph node enlargements. The diagnostic work up revealed multiple lymph nodes enlargement at the thoraco-abdominal level that were histologically characteristic for a large immunoblastic B cell lymphoma in the context of a serological HBV positivity. Methotrexate was immediately stopped and a rituximab based chemotherapuy was started with subsequent complete remission of the lymphoma. For the first time in two years the patient did not experienced a UC flare in the absence of any classical immunomodulatory or steroid therapy. A total procotocolecotomy performed one and half month later confirmed that the whole colon was macro- and microscopically normal, with the absence of any signs of acute or chronic inflammation such as plasmolympohytic infiltrates. The patient still remains, 2 years later, in complete remission of her lymphoma. This report gives evidence for the involvement of B cells in the pathophysiology of UC and support in favor of anti- B cell based therapy such as rituximab as a new potential therapeutic weapon in UC.

LOCAL INJECTION OF INFILXIMAB IN CROHN’S DISEASE RECURRENT: A PILOT PROSPECTIVE LONGITUDINAL STUDY IN THE LONG-TERM

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Aim: We aimed to assess the long-term safety and clinical efficacy of local IFX injection into CD recurrence. We also investigated the short-term safety and efficacy in additional CD pts.

Methods: In an open-label study, 14 clinically inactive CD pts with previous ileo-colonic resection requiring colonoscopy (CC) were enrolled. Long-term study. The same 8 CD pts assessed and reported in the short-term study were followed up and assessed in the long-term. Short-term study. Additional 6 CD pts were injected with IFX at the site of recurrence with timing of CC related to the patient’s compliance. Inclusion criteria: localized (<5cm) CD recurrence, inflammatory pattern, inactive CD. The endoscopic recurrence was graded according to Rutgeerts score. In all the 14 pts all the involved area was injected with IFX. Long-term study. Among the 8 pts, CC after the first injection was performed at 2 wks in 4 pts (3 performing a second injection followed by CC at 6 wks), at 4 wks in 4 pts (2 performing a second injection followed by CC at 8 wks). Short-term-study. Among the 6 pts, CC after first injection was performed at 6 (n=3), 12 (n=1), 16 (n=1) and 28 wks (n=1).

Results: No pts showed local or systemic side-effects or clinical relapse in the short and long-term. Long-term study. Among the 8 CD pts, 6 remained followed up > 2 months after the first injection, all 6 pts maintaining clinical remission from the injection to the follow up end (median 4 months range 1-32). Short-term study. All the 6 pts maintained clinical remission at the fol-
low up end (median 6 mths, range 1-14). Recurrence score before and after injection was unchanged in 4, increased in 1, improved in 1 patient.

Conclusions: Present findings suggest the long-term safety of local Infliximab injection into CD recurrence

P084 SEVERITY OF CROHN’S DISEASE RECURRENT AFTER ILEO-COLON RESECTION: CORRELATION BETWEEN ENDOSCOPIC SCORE AND SONOGRAPHIC FINDINGS

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Background: ileocolonoscopy (IC) is the gold standard for assessing Crohn’s Disease (CD) post-operative (PO) recurrence. Small intestine contrast ultra-sonography (SICUS) is able to visualize small bowel wall and extraluminal lesions in CD, while colonoscopy shows mucosal lesions. Whether SICUS and IC are comparable in the assessment of CD PO-recurrence is unknown.

Aims: To investigate the usefulness of SICUS for assessing CD PO-recurrence. Specific aim was to assess correlation between CD recurrence severity assessed by sonographic bowel wall thickness and endoscopic Rutgeerts’ score.

Methods: 48 pts with ileo-colonic resection, requiring IC were enrolled. All 48 pts underwent both IC and SICUS within 6 mths; 6 pts repeated the 2 procedure. Results from 54 procedures were compared. IC was performed by the same endoscopist using Rutgeerts’ score. SICUS was performed after PEG ingestion by the same sonologist, considering findings compatible with recurrence increased bowel wall thickness, dilation and stricture. The correlation between the severity of recurrence assessed by the 2 techniques was searched by using sonographic peri-anastomotic bowel wall thickness and the endoscopic Rutgeerts’ score. The sonologist was unaware of the endoscopic findings. The coefficient of correlation was assessed, while the x2 test was used for assessing concordance in terms of detection of recurrence using the two techniques.

Results: Endoscopic recurrence was detected in 49/54 (91%) procedures. Sonographic findings compatible with recurrence were detected in 50/54 (92.5%). When assessing the correlation between the severity of PO-recurrence by using the two techniques, the peri-anastomotic bowel wall thickness as assessed by SICUS was significantly correlated with the Rutgeerts’ score (p=0.002; r=0.417). Conclusions: Although SICUS and IC detect different views of the bowel, a significant correlation is observed between these 2 techniques in the assessment of presence and severity of recurrence. SICUS may be used as an alternative non-invasive technique for assessing CD PO-recurrence

P085 VISILIZUMAB FOR THE TREATMENT OF SUBJECTS WITH INTRAVENTOUS STEROID-REFRACTORY ULCERATIVE COLITIS (IVSR-UC): SHORT AND LONG-TERM DISEASE RESPONSE SIMILAR OVER MULTIPLE DOSE LEVELS


Purpose: This open-label clinical trial investigated the safety and efficacy of visilizumab, a humanized anti-CD3 monoclonal antibody, in hospitalized subjects with IVSR-UC. Four dose levels (5, 7.5, 10 or 12.5 mg/kg) were studied to determine the optimal clinical activity of visilizumab relative to its safety profile.

Methods: Seventy-three UC subjects (male: 42; female: 31; pancolitis: 48, left-sided colitis: 25) were enrolled. All subjects were administered IVSR-UC with visilizumab 5, 7.5, 10 or 12.5 mg/kg intravenous doses of visilizumab on days 1 and 2. Safety was evaluated by the incidence of adverse events (AEs) and time to T-cell recovery. All AEs occurring on days 1 through 3 were considered to be associated with visilizumab-related syndrome (CRS). Efficacy was assessed on day 30 by Mayo score; a response was defined as a 3 point reduction from baseline, and a remission as a total Mayo score ≤ 2.

Results: The mean baseline Mayo score was 10.4. Mild to moderate CRS symptoms occurred in 92% of all subjects, with no apparent dose effect (range: 83% to 100%). However, the incidence of grade 3 and 4 (severe; life-threatening) CRS AEs was lower in the 5 mcg/kg dose group (0%) compared with the higher dose groups (27%). One subject in the 10 mcg/kg dose group reported a grade 4 AE on day 2 (atrial fibrillation); this subject recovered by the following day with medication. Several cases of delayed recovery of CD4 positive T-cell levels were reported in the higher dose groups, but none in the 5 mcg/kg group. No lymphoproliferative AEs were reported. Grade 3 AEs were reported in 41% of the lowest dose group and in 59% (range: 83% to 100%) of the other AEs. AEs included infection (10%), gastrointestinal AEs (10%), and mucocutaneous AEs (10%). Overall, 29% of subjects underwent a colectomy prior to day 31. Thirty-eight percent of all subjects that have been followed for at least 315 days required no salvage therapy during this time period. No significant differences were observed among dose groups in time to disease progression.

Conclusion: All visilizumab doses studied were tolerated and induced a rapid and sustained response in the majority of IVSR-UC subjects. T-cell recovery times and the severity of CRS symptoms were more favorable in the 5 mcg/kg dose group. Visilizumab 5mcg/kg appears to be safer while demonstrating similar activity compared with the higher doses tested.

P086 THERAPEUTIC EFFICACY AGAINST MURINE DSS-INDUCED COLITIS OF TWO GENE TRANSFER VECTORS INDUCING GENERALIZED IL-10 OVEREXPRESSSION

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The efficacy of systemic administration of IL-10 for the treatment of intestinal inflammation has been assayed both in animal models of colitis and in clinical trials involving IBD patients. In studies such as the therapeutic efficacy of IL-10 has been found to be limited, and our results strongly suggest that its quick degradation after intravenous injection. We intended to compare the therapeutic effects of two alternative strategies capable of induce high blood levels of IL-10 in a murine model of IBD. Type 5 adenovirus (Ad5) carrying the murine IL-10 gene (mIL-10) and a CGG-free plasmid carrying mIL-10 gene were intravenously given to C57BI/6 mice. Colitis was induced by adding 3% DSS to drinking water for 5 days. In this strain DSS causes a chronic colitis which bears more resemblances to human IBD than that developed in other mouse strains such as BalbC. Eighteen hours before exposure to DSS, either vehicle, Ad5IL10 or P-IL10 were given by i.v. route. Disease activity index was calculated according to a previously established score. Myeloperoxidase activity, colon length and microscopic colonic injury were determined at the end of the experiment (7 and 15 days after DSS). Both vectors caused a significant amelioration of disease activity index as well as colonic myeloperoxidase activity, colonic shortening, and microscopic damage score. Early amelioration was similar with both vectors but some mortality was found in Ad5ILm10-10 group 8-11 days after DSS, suggesting that a generalized overexpression of IL-10 over long periods may not be desirable for it can result in a delayed immunodepression. Thus, blood levels of IL-10 may not bear a linear relationship with therapeutic efficacy. Our results strongly suggest that local rather than generalized overexpression of anti-inflammatory mediators should be sought to address treatment of intestinal inflammation.

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P087 BIOSAFETY AND BIODISTRIBUTION OF CHIMERIC ADENOVIRUSES TO THE GASTROINTESTINAL TRACT: A NEW APPROACH TO SELECTIVE GENE DELIVERY TO THE INTESTINE

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The lack of vectors for selective gene delivery to the intestine has hampered the development of gene therapy strategies for IBD among other chronic intestinal diseases. We hypothesized that chimeric adenoviruses (Ad) build up with a combination of the extensively studied Ad5 (serotype C) together with Ad40 (serotype F) might hold the intestinal tropism of the F serotype and thus might be useful as delivery vectors for gene delivery to the intestine. The biosafety and biodistribution of several chimeric adenoviruses were tested in healthy CD-1 mice (oral, rectal and intravenous routes). The animals were euthanized 3 days after adenovirus administration. The expression of the reporter gene LacZ was measured in extracts of 15 different organs by luminometry and thus might be useful as delivery vectors for gene delivery to the intestine.