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Infliximab in Hispanics: Characterization of Response to Infliximab in an Ethnic Minority with Crohn's Disease

JOSÉ M. SÁNCHEZ, MD; JUAN C. MALDONADO, MD; ESTHER A. TORRES, MD; CYNTHIA RIVERA, MPH

Purpose: The incidence and prevalence of Crohn' s disease (CD) varies geographically and with racial/ ethnic background. The highest frequency of occurrence is in North America and Northern Europe. Incidence is highest among Caucasians, lower in blacks and Hispanics, and lowest in Asians. However in the mid-1980s and 1990s, the incidence and prevalence increased in continental Europe, the Middle East, the Pacific Rim, Africa, and Latin America. An increase in the incidence of CD has been noted in Puerto Rico, although our population differs genetically from other described CD populations. A study in our population showed lower prevalence of ASCA and no NOD2 in our CD patients. Infliximab, a TNFa antibody, is effective in refractory inflammatory CD and in fistulizing disease. Since limited data exists regarding CD in Hispanics, the fastest growing minority group in the United States, we designed this retrospective study with patients treated with infliximab at our institution. We wanted to determine if the response to infliximab in genetically admixed Hispanics differed from that previously reported.

Methods: Baseline characteristics, infusion related information and clinical response was abstracted from medical records. Clinical response was classified as complete response, partial response, and nonresponse.

Results: The study included 15 patients treated for refractory inflammatory disease, 9 for fistulizing disease, and 11 for both. The positive response rate was 83%(29/35) and the non response rate was 17%(6/35). Overall the patients with complete, partial, and no response were 13/35(37%), 16/35(46%), and 6/ 35(17%), respectively. No statistically significant association was found between response and disease location. Significant association was found between response and fistula type (p=0.02). Steroid withdrawal was possible in 21/31 patients (68%). In terms of safety, 9/35 patients (26 %) suffered an adverse reaction, 4 patients required therapy discontinuation.

Conclusion: This study suggests that infliximab has similar global response, allowance of steroid withdrawal and safety in Hispanics as in other populations. Ethnicity does not seem to influence response rate to infliximab.

Key words: Crohn's disease, Infliximab, Hispanics

Crohn's disease (CD) is a chronic, recurrent inflammatory disease that may involve any segment of the gastrointestinal tract from the mouth to the anus. CD is characterized by segmental, transmural inflammation with or without mucosal granulomatous lesions and fistula formation. One third of cases of Crohn's disease involve only the small bowel, most commonly the terminal ileum. Half of cases involve the small bowel and colon, most often the terminal ileum and proximal ascending colon. In 20 % of cases only the colon is affected. This disease seems to result from an abnormal overreacting immune response to an environmental antigen in a genetically susceptible individual (1).

The first line treatment for patients with mild to moderate CD is oral and topical aminosalicylates such as sulfasalazine and mesalamine (2). Corticosteroids are effective in suppressing symptoms in severe disease, but their use is limited by short- and long-term side effects (2, 3). Antibiotics such as metronidazole and ciprofloxacin have shown short-term effectiveness in fistulizing perianal disease (2). Treatment with antimetabolites such as methotrexate, azathioprine, cyclosporine, or 6-mercaptopurine have been shown to be effective in patients with refractory inflammatory disease or those dependent on corticosteroids in order to avoid their secondary effects (4-8). These agents have also been

From the Division of Gastroenterology and Liver Diseases, Department of Medicine, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

Address correspondence to: Esther A. Torres, MD, Department of Medicine A-838, University of Puerto Rico, School of Medicine,Medical Sciences Campus, PO Box 365067, San Juan, P.R. 00936-5067.

associated with improvement and healing in fistulizing and perianal CD (4-6, 9). Since the chronic inflammation in Crohn's disease can be attributed to the increased production of inflammatory cytokines (10), inhibition of these molecules has been suggested as an alternative treatment for unresponsive patients.

The cytokine TNF-a is thought to be involved as a mediator of inflammation in CD. Patients with CD have an increased number of lamina propria cells producing TNF-a (10), and increased stool excretion of this cytokine (11). This molecule results in the activation of macrophages and neutrophils, and increased permeability of mucosal epithelium (12). The proteases, prostaglandins, leukotrienes and eicosanoids produced by inflammatory cells lead to tissue injury. Some of these products may also enhance mucosal secretion of chloride and potassium contributing to the development of diarrhea (12). Infliximab, a murine chimeric anti- tumor necrosis factor-a (TNF-a) antibody, has shown efficacy in the treatment of moderate to severe inflammatory disease and in fistulizing disease (13-20).

Infliximab with its TNF-a antagonistic activity, as well as cytotoxicity against immune cells and induction of T-cell apoptosis, has been a focus for clinical research in inflammatory diseases. Studies in patients with rheumatoid arthritis indicated that this agent had potent and effective anti-inflammatory activity in patients with high disease activity (21, 22). This finding made infliximab an appropriate candidate for treatment of Crohn's disease. Direct evidence that TNF-a inhibition by infliximab can benefit patients with Crohn's disease was first reported by Van Dullemen *et al.* in 1995 (13). Later, in a randomized, placebo- controlled trial, Targan *et al.* reported 50% to 80% response rates and 25% to 48% remission rates at 4 weeks after a single infusion of infliximab of 5, 10, or 20 mg/kg of body weight (14). The clinical response was paralleled by endoscopic and histological healing (15). The efficacy and safety of repeated infliximab infusions for maintenance therapy was first reported by Rutgeerts *et al.* after obtaining a 53 % remission rate (20% in placebo group) at 44 weeks after the last infusion (16). The large, multicenter ACCENT I clinical trial supported the efficacy of infliximab as a maintenance therapy for CD (17). Studies have also suggested that infliximab has steroid-sparing properties (13, 17, 18) as well as effectiveness in fistulizing CD (18, 19). The results reported in the ACCENT I trial allowed infliximab to receive FDA approval in 1998 for the treatment of moderate to severely active Crohn's disease to reduce signs and symptoms in patients with inadequate response to conventional therapy. Approval was also given for patients with fistulizing Crohn's disease to reduce the number of draining enterocutaneous fistula(s).

The incidence and prevalence of Crohn's disease varies geographically and with racial/ethnic background. The highest frequency of occurrence is in North America and Northern Europe. Incidence is highest among Caucasians, lower in black and Hispanics, and lowest in Asians. However in the mid-1980s and 1990s, the incidence and prevalence increased in continental Europe, the Middle East, the Pacific Rim, Africa, and Latin America. CD is an increasingly frequent diagnosis in Puerto Rico, with a prevalence of 41.3/100,000 noted in a preliminary study in 1996 (23). Studies in our population showed lower prevalence of ASCA and no NOD2 in our CD patients as compared to that reported in Caucasian populations (24-26). These findings suggest that there maybe other genes that are predominantly associated with CD in our population. These findings also favor a heterogenicity in the pathogenesis of CD in Puerto Ricans. Since limited data exists regarding CD in Hispanics, the fastest growing minority group in the United States, we designed this retrospective study of patients treated with infliximab at our institution. Our aim was to determine if the proposed pathogenic heterogenicity of CD in our population alters the response to infliximab in the genetically admixed Hispanics as compared to the reported response in Caucasians. The efficacy and safety of infliximab was described in terms of clinical outcome, steroid withdrawal, and adverse events in patients with refractory inflammatory CD and/or fistulizing CD.

Materials and Methods

Approval by the Institutional Review Board (IRB) of the University of Puerto Rico Medical Sciences Campus was received before starting data collection. Medical records of patients from the University of Puerto Rico Inflammatory Bowel Disease Service (UPR-IBD Service) treated with infliximab were obtained. Patients from our clinics who received infliximab infusions at centers other than the University Hospital ("outside") were also included in the study. Records were reviewed and baseline characteristics of patients were recorded in a questionnaire similar to that used by Ricart *et al.* (18). The investigators that reviewed the medical records were the physicians of the patients included in the study. Questionnaires were identified only with numerical codes to avoid identification of patients and maintain the confidentiality and privacy of the patient's medical information. Questionnaires were stored under password-protected lock. Questionnaires from patients infused at the University Hospital and those from other infusion centers were labeled as group A and group B, respectively. Baseline characteristics included: demographic information, duration of CD, anatomical

distribution of CD, prior and concomitant medical treatment(s) of CD, surgical intervention(s) related to CD before and during the treatment with infliximab, previous medications, and concomitant medications. Infusion-related information recorded included indication for infliximab treatment, geographic site of infusions, number of infusions, dose of infusions, intervals between infusions, premedication, and clinical response. Since we were not able to document adverse events in patients receiving the infusions outside, adverse events were evaluated in the University Hospital subgroup.

The study includes all the patients treated with infliximab from January 2002 to December 2003. Infliximab infusions are being prescribed in our center since January 2002. Induction therapy of infliximab consists of 5 mg/kg given at 0, 2, and 6 weeks. Maintenance therapy of 5 mg/kg is given every 8 weeks. Doses are modified according to patient's response. Infusions are administered by certified nurses and the center is under continuous supervision by a physician. Patients are closely monitored during the infusion and post-infusion period in order to detect the development of any adverse reaction. The center has the appropriate medications to manage any anaphylactic reaction. Premedication with corticosteroids and antihistaminics is given to patients with history of allergic-type adverse reactions during previous infusions. Information related to disease evolution and any infusion related event is recorded in the medical record of each patient. Patients receiving infliximab infusions at other infusion centers were also included in the analysis.

To determine clinical response the three categories defined by Ricart *et al.* (18) were used: complete response, partial response, and non response. A complete response is defined as a complete cessation of fistula drainage and total closure of all fistulae and/or cessation of abdominal cramping and diarrhea. A partial response is defined as a reduction in the number, size, drainage or discomfort associated with the fistula, and/or decrease of abdominal cramping and diarrhea. All other outcomes are defined as non response. We also determined the number of patients with successful withdrawal from other medications, and those who achieved remission of the disease. Treatment resistance was assessed; this was defined as patients requiring more than 5 mg/kg doses or those requiring shortened intervals of infliximab infusions.

Descriptive statistics for continuous variables including means, standard deviation, median and range (min.-max.) were computed. Frequency distributions and percents were used for categorical variables. The Shapiro Wilk test was used to verify the normal assumption of quantitative variables, as well as box-plots and quantile plots. The Pearson's chi-square test or Fisher's exact test, when appropriate, was used to determine statistical associations among categorical variables. The unadjusted odds ratios (OR) and 95% confidence interval were used to determine the magnitude of these associations. The Student t-test or Mann-Whitney test, when appropriate, were used to compare the means of quantitative variables. The analysis of variance (ANOVA) or Kruskal Wallis, when appropriate, was used to compare the means of quantitative variables for more than two groups. Polytomous Logistic Regression was performed to explain the clinical response (complete response, partial response and non-response) with the smoking and concomitant medications variables, adjusted by gender and age. Data entry was performed using Epi-Info 6.04d. The SAS and STATA packages were used to perform the statistical analysis.

Results

The study included 35 patients; 21 were male and 14 were female. The age of patients ranged from 12 to 74 years old with a mean of 31.7 ± 12.8 years. Demographic characteristics of patients and medical history are summarized in Table 1. Information includes demographic information, duration of CD, anatomical distribution of CD, prior and concomitant medical treatment(s) of CD, surgical intervention(s) related to CD before and during the treatment with infliximab, previous medications, and concomitant medications. Subgroup A was composed of 18 patients and subgroup B of 17 patients. The median time since first infusion until the time of record review (follow-up time) in subgroup A was 8.5 months. We were not able to accurately determine follow-up time in subgroup B.

Of the 35 patients, 15 were treated for refractory inflammatory disease, 9 for fistulizing disease, and 11 for both diseases. The positive global response rate was 83% (29/35) and the non response rate was 17% (6/35). Complete response was seen in 13/35 (37%), partial and no response were seen in 16/35 (46%) and 6/35 (17%), respectively. In patients treated for fistulizing disease, 4/9 (44%) had complete response, 4/9 (44%) had partial response, and 1/9 (11 %) had no response. The complete, partial and no response in patients with refractory inflammatory disease were 5/15 (33%), 7/15 (47%), and 3/15 (20%) respectively. In patients with refractory and fistulizing disease, 4/11 (36%), 5/11 (45%), and 2/11 (18%) had complete, partial, and no response respectively. Table 2 summarizes response by disease type. Neither disease type nor disease location were found to have a significant association with response. From a total of 30 perianal fistulae, 67% had complete response and 27%had partial response, 7% did not respond. Two of 3 rectovaginal fistulae had partial

Table 1. Baseline Characteristics of the Patients

Age (yr): range 12-74 median 29 mean 31.7 mode 36
Gender: male 21 female 14
Current cigarette smoker (n) Yes 5 No 30
Duration of CD (yr): range 1-27 median 7 mean 8.7 mode 4
Disease location (n)
- Small Bowel 9
- Colon 10
- Small bowel and Colon 12
- Rectum 10
- Ileal Pouch 1
- Perianal 17
- Upper GI tract 3

Patient with fistula: 20
- Number of fistulae (n) 40
- Location of fistulae (n, %)
  - Perianal n=30 (Patients: 15)
  - Other n=10 (Patients: 8)

Rectovaginal 3 enterovesical 4 colonic-cutanous 3
Patients with extraintestinal manifestations (n): 12 (extraintestinal manifestations n=15)
- Peripheral arthritis 6
- Erythema nodosum 6
- Oral aphthous ulcers 3

Patients with previous surgery for CD: 21
- Previous surgery for CD (n): 41

Patients with previous resections/fistula repair (n): 15
Previous resections/fistula repair (n): 21
Current home total parenteral nutrition (n): 0
Patients with previous medication: 34
- Previous medications (n):
- Aminosalicylates 31
- Corticosteroids 31
- 6-MP/AZA/MTX 7/23/6
- Antibiotics 27
- Other 1

Patients with concomitant medications: 33
- Concomitant medications (n):
- Aminosalicylates 15
- Corticosteroids 10
- 6-MP/AZA/MTX 3/21/3
- Antibiotics 7

response and 1 no response. Two of 4 enterovesical fistulae completely responded and 2 partially responded; 1 of 3 colocutaneous fistulae had a complete response and 2 did not respond (Table 3). A significant association was found between response and fistula type (p=0.02). The observed trend is for a better response in perianal fistula as reported

Table 2. Response to Infliximab Therapy

	Overall n (%)	Fistulizing n (%)	Refractory n (%)	Both n (%)
Complete response	13(37)	4(44)	5(33)	4(36)
Partial response	16(46)	4(44)	7(47)	5(45)
Non-response	6(17)	1(11)	3(20)	2(18)

Table 3. Response by Type of Fistula

Type of fistula	Number of fistula	Complete response n (%)	Partial response n (%)	Non-response n (%)
Perianal	30	20(67)	8(27)	2(7)
Rectovaginal	3	0	2(67)	1(33)
Enterovesical	4	2(50)	2(50)	0
Colocutanous	3	1(33)	0	2(67)
Total	40	23(57.5)	12(30)	5(12.5)

in most studies. The small number of other types of fistulae prevent conclusions about which one is related to a better response.

Steroid withdrawal was possible in 21/31 patients (68%, Table 4). Patients with fistulizing and refractory

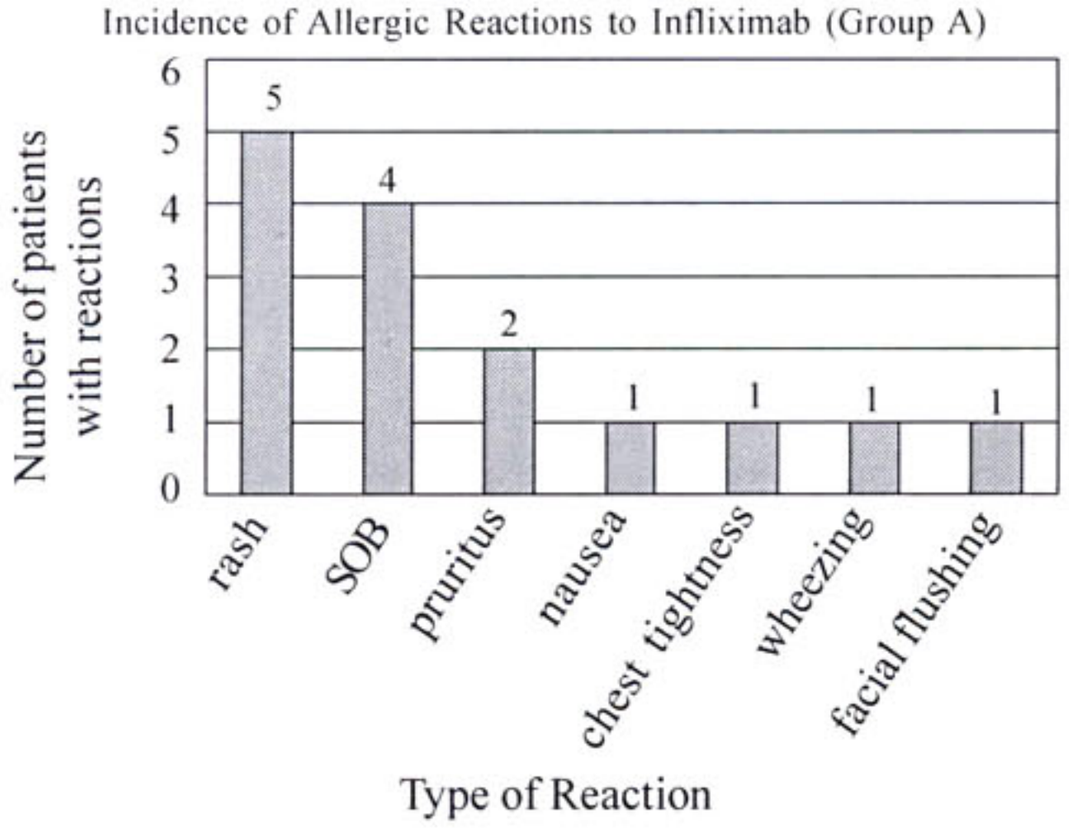
Table 4. Steroid Withdrawal

	Overall n (%)	Fistulizing n (%)	Refractory n (%)	Both n (%)
Withdrawn from steroids	21(68)	4(67)	8(57)	9(82)
Not withdrawn from steroids	10(32)	2(33)	6(43)	2(18)

inflammatory disease had a steroid withdrawal rate of 67% and 57% respectively (p=0.25). Seven patients with treatment resistance are in a modified infusion scheme: 3 require a 10 mg/kg dose, and 1 requires a 15 mg/kg dose. In three patients the interval between infusion was shortened to 6 weeks in order to sustain a response.

In terms of safety, 9/35 patients (26 %) suffered an adverse reaction, 4 patients required therapy discontinuation. Although we were able to identify patients that suffered adverse events and/or therapy

Figure 1. Incidence of Adverse Events in Subgroup A



discontinuation, the adverse reactions could be described only in subgroup A. In subgroup A, 7/18 patients (39%) had adverse reactions. In four of them therapy was discontinued, and two were premedicated before infusions.The reactions seen are shown in Figure 1. No fatal otcomes resulted from infliximab treatment.

Discussion

Previous studies have established the effectiveness and safety of maintenance treatment with infliximab at a dose of 5 mg/kg administered at 8 weeks intervals (17). The primary purpose of this study was to determine if the response to infliximab in genetically admixed Hispanics differed from that previously reported. This study suggests that infliximab has similar global response, allowance of steroid withdrawal and safety in Hispanics as in other populations. Hispanic ethnicity does not seem to influence response rate to infliximab.

Our results are similar to those obtained by Hanauer and colleagues in the ACCENT I trial (17). In this study, 40% of patients were in remission and 67% had a reduction in the Crohn's Disease Activity Index (CDAI) of more than 70 points after 10 weeks of follow-up. This includes patients with either 5 mg/kg dose or 10 mg /kg dose. After 54 weeks, 43% of patients receiving 5 mg/kg maintained a clinical response versus 53% in those receiving a 10 mg/kg dose. Although results are comparable with those obtained in our study, it is important to emphasize that different response criteria were used. We did not use the CDAI and the response rate was not determined on the basis of follow-up time. In this study 29% of patients receiving infliximab maintenance had discontinued corticosteroids while in clinical remission. This is lower than that obtained in our study, but the difference can be explained in terms of different criteria used to discontinue steroids. In ACCENT I, steroid withdrawal was done after clinical remission was documented by a CDAI <150 points. In terms of safety, 23% and 19% of patients receiving 5 mg/kg and 10 mg/kg, respectively, suffered infusion related reactions. The most common reactions were headache, nausea, injection site irritation, flushing, chest pain, dyspnea, and pruritus. These numbers do not include serious adverse events and serum sickness-like reactions. In our patients 26% suffered adverse events, and 4 patients had therapy discontinuation.

The differences in clinical response characterization in our study, similar to that of Ricart and colleagues (18), and in the ACCENT I trial (that used the CDAI score), as well as the possibility of different criteria for both steroid discontinuation and infliximab discontinuation may explain the difference in the obtained results. A more comparable analysis can be made with the data obtained by Ricart *et al.* at the Mayo Clinic (Table 5). In their study, a positive global response was seen in 72% of patients and non-response rate was 28%. The positive response rates in patients with refractory inflammatory disease, fistulizing disease, and both diseases were 72%, 65%, and 85%, respectively. In our study a 83% global response was obtained, with positive response in 80%, 88%, and 81% of patients with inflammatory, fistulizing, and both diseases, respectively. From a total of 74 fistulae, Ricart reported a positive response of 60.8%, with 68% positive response for perianal fistulae (34/50). We had an 87.5% global positive response. The most common type of fistula was perianal, and the positive response rate was 94%. The main difference between the results of Ricart and ours, noted in most response categories reported, is the increase in partial responses obtained in our series compared to Ricart's. This may be due to an intrinsic difference in response, but most likely is the result of the lack of accurate

Table 5. Comparison Between the University of Puerto Rico and the Mayo Clinic

	UPR-IBD (%)	Mayo Clinic (%)
Patients	**35 (n)**	**100 (n)**
Positive global response	83	72
Complete	37	50
Partial	46	22
Nonresponse	17	28
Positive response in inflammatory disease	80	72
Complete	33	52.5
Partial	47	19.5
Nonresponse	20	28
Positive response in fistulizing disease	88	65.4
Complete	44	34.6
Partial	44	30.8
Nonresponse	11	34.6
Positive response if both diseases	81	85.5
Complete	36	69
Partial	45	15.5
Nonresponse	18	15.5
Total of fistulae	40 (n)	74 (n)
Positive response to fistula	87.5	60.8
Complete	57.5	48.6
Partial	30	12.2
Nonresponse	12.5	39.2
Positive response to perianal fistula	94	68
Complete	67	56
Partial	27	12
Nonresponse	7	32
Steroid withdrawal	68	73
Infusion- related reactions	26	19

and specific information obtained from records. This could be clarified by interviewing the patients during an evaluation encounter or by phone. Our study was restricted to medical record review only. Steroid withdrawal in Ricart's series was achieved in 73% of patients, very similar to our result of 68%. Ricart reported infusion related reactions in 19% of patients (versus 26% in our study). The most common reactions were chest pain, shortness of breath, fever, flu-like symptoms, and myalgias.

In conclusion, infliximab seems to have similar global response in Hispanics as in other populations. In addition, no difference was noted in the percent of patients in which steroid withdrawal was achieved. Safety results were also comparable to those reported in other series. Incidence of infusion related reactions and type of reactions were similar in the UPR-IBD service and in other studies. Finally, ethnicity does not seem to influence response rate to infliximab.

Resumen

Propósito: La incidencia y prevalencia de la enfermedad de Crohn (CD) varia geográficamente y de acuerdo a factores raciales y étnicos. Esta se encuentra con mayor frecuencia en Norte América y Europa del Norte. La incidencia es mayor en caucásicos que en negros e hispanos, siendo los asiáticos el grupo con menor incidencia. Sin embargo, a mediados de 1980s y 1990s, la incidencia y prevalencia aumentaron en Europa continental, el Este Medio, la costa del Pacífico, Africa y América Latina. Este aumento en incidencia también se ha observado en Puerto Rico, aunque nuestra población difiere genéticamente de otras poblaciones con CD descritas. Un estudio previo en nuestra población mostró una menor prevalencia de ASCA y ausencia de NOD 2 en nuestros pacientes con CD. Infliximab, un anticuerpo contra TNFa es eficaz en el tratamiento de CD tanto en enfermedad inflamatoria refractaria como en enfermedad fistulizante. Debido a la limitada información que tenemos acerca de CD en hispanos, la minoría con mas rápido crecimiento en Estados Unidos, hemos diseñado este estudio retrospectivo con pacientes tratados con infliximab en nuestra institución. Deseamos determinar si la respuesta a infliximab en hispanos genéticamente mixtos difiere de los reportados previamente en otras poblaciones.

Métodos: Las características de la población, la información relacionada a las infusiones y la respuesta clínica fueron extraídas de los expedients clínicos de los pacientes. La respuesta clínica se clasificó como respuesta completa, respuesta parcial y no respuesta

Resultados: El estudio incluyó 15 pacientes tratados por enfermedad inflamatoria refractaria, 9 por enfermedad fistulizante, y 11 por ambas. La respuesta positiva fue 83%(29/35) y la no respuesta fue 17%(6/35). Globalmente los pacientes con respuesta completa, parcial y no respuesta fueron 13/35(37%), 16/35(46%) y 6/35(17%), respectivamente. No se encontró asociación significativa entre respuesta y localización de la enfermedad. Sin embargo se encontró una asociación significativa entre respuesta y tipo de fístula (p=0.02). La retirada de esteroides fue possible en 21/31 pacientes (68%). En términos de seguridad, 9/35 pacientes (26 %) sufrieron alguna reacción adversa, en 4 pacientes la terapia tuvo que ser descontinuada.

Conclusión: Este estudio sugiere que la respuesta global, el potencial de retirada de esteroides y la seguridad de infliximab en hispanos son similares a los reportados en otras poblaciones. La etnicidad no parece influenciar la respuesta a infliximab

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