

Adalimumab and Infliximab in Crohn's disease - real life data from a national retrospective cohort study

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ABSTRACT: Aim: to compare the efficacy and safety of Adalimumab(ADA) and Infliximab(IFX), in a large Romanian population and to identify predictors of response. Methods We performed a national retrospective cohort study including 265 patients (136 ADA, 129 IFX) between 2008-2014. Binary logistic regression was performed with the statistical program Minitab. Results: Patients were half women, with a median age of 36, a median disease duration of 2.5 years, 80% received Azathioprine. Mean therapy duration was 20 months in ADA group and 36 months in IFX group. Complete response to Adalimumab respectively Infliximab was recorded in 77%vs.65%, secondary loss of response in 18%vs.28%, statistically comparable. We failed to identify predictors of response. In 79.2%of patients with secondary loss of response to ADA, the dose was escalated, 12.5% were switched to Infliximab. In 70%of patients that lost response to IFX, the dose was increased, 30% were switched to Adalimumab. Conclusions: Adalimumab and Infliximab have similar efficacy, with a complete response rate of~70%. In case of secondary loss of response to IFX, the best solution is to switch to ADA, with 83% response rate, while in case of secondary loss of response to ADA, increasing the dose leads to 84 % response rate.

KEYWORDS: Adalimumab, Infliximab, Crohn's disease

Introduction

Crohn's disease (CD) is a lifelong disease arising from an interaction between genetic and environmental factors, but predominantly observed in developed countries of the world. The precise etiology is unknown, therefore a causal therapy is not yet available. [1]

Remission is widely accepted as a CDAI of less than 150 points and response is increasingly defined as a decrease in CDAI by ≥ 100 points [1]. Relapse is a flare of symptoms in a patient with established CD who is in clinical remission (CDAI of more than 150 with an increase of more than 70 points) [2]

Patients with Steroid-refractory disease are those who have active disease despite prednisolone of up to 0.75 mg/kg/day over a period of 4 weeks. Steroid-dependent disease is defined either in patients who are unable to reduce steroids below the equivalent of prednisolone 10 mg/day (or budesonide below 3 mg/day) after 3 months of starting steroids, without recurrent active disease, or in patients

who have a relapse after 3 months of stopping steroids. [1]

Mucosal healing evaluated through endoscopy is a surrogate marker of sustained controlled Crohn's disease [3]

Infliximab (IFX, Remicade®) a chimeric immunoglobulin G (IgG) human (75%)/murine (25%) mAb administered by intravenous infusion, is indicated for induction and maintenance of remission in adult and pediatric CD [4].

Adalimumab (ADA, Humira) is a self-injected, fully humanized recombinant mAb. This agent is indicated for induction and maintenance of remission in adult CD. IFX and ADA have high binding affinity for both soluble and transmembrane forms of TNF, blocking interaction of TNF with p55 and p75 cell surface TNF receptors and neutralizing its biologic activity [5, 6]. In Romania, the use of IFX for CD has an experience of more than a decade.

Data regarding IFX use in CD come from randomized trials: ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a

New Long-term Treatment Regimen) I and II established the use of IFX for active maintenance, and fistulizing CD [7,8,9].

The purpose of this study was to evaluate whether Infliximab and Adalimumab achieve expectations in clinical practice in Romania: a country in eastern Europe where the incidence and prevalence of Crohn's disease is lower than in eastern Europe, and the proportion of moderate-severe cases is much lower [10, 11].

Material and methods

A retrospective cohort study was performed, enrolling all patients with Crohn's disease in Romania treated with Infliximab and with Adalimumab in a period of 5 years (august 2008-august 2013). All these patients were biological naïve. The data were collected from each patient's files existing in the archive of the National Insurance Agency. All subjects included signed an informed consent stating that their data can be used in scientific purposes and the study was approved by the Regional Ethical Comitee.

All patients that stopped therapy were questioned regarding the reasons for stopping therapy by- phone or mail or e-mail.

According to Romanian guidelines, patients eligible for therapy with biologic agents are adults or children (6 to 17 years) with moderate-severe Crohn's disease with inadequate treatment response or intolerance to standard therapy (corticosteroids, azathioprine/6-Mercaptopurine, Methotrexate) or cortico-dependent, those with fistulizing CD non-responsive to conventional therapy (presumed non-having abscesses).

All patients received induction therapy with Infliximab 5 mg/kg 0,2,6 weeks, followed by maintenance therapy: 5 mg/kg at 8 weeks. If the subject loses the response, the interval between the doses is shortened at 6 or 4 weeks, or the dose is doubled to 10 mg/kg at 4 weeks at the indication of his physician-gastroenterologist.

Patients on adalimumab received two induction doses (160 mg or 80 mg and 80 or 40mg subcutaneously [sc]) at weeks 0 and 2, respectively and maintenance (40 mg sc every other week) therapy. At or after eight weeks, patients with flare or nonresponse would have their dosage increased to 40 mg sc weekly.

Their diagnosis was confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. Patients were classified according to Montréal phenotype classification [12].

The recorded informations were: type of disease, age, sex, time of disease prior to IFX or ADA therapy, and location of CD (terminal ileum and colon, colon only, or ileum/small bowel only). Smoking history was poorly recorded and therefore omitted. Laboratory data were recorded in three periods to assess changes: within 1 month prior to IFX therapy, at 6 weeks after the first infusion and then at 6 months in the maintenance period.

Relevant therapeutic data before IFX were recorded: either no therapy, either prednisone, either azathioprine. Azathioprine (AZA) was used at the standard dose of 2-2.5 mg/kg/day. Information on the intake of medications other than IFX after the start of infusion was recorded inconsistently and was therefore omitted from analysis. However, previous surgical interventions and the presence of external fistulae were recorded, as well as side effects.

We didn't have data regarding therapeutic drug monitoring in monoclonal therapy (trough serum infliximab levels and antibodies toward infliximab).

Screening for active infection and for latent tuberculosis (chest X-ray and cutaneous PPD test or Quantiferon) was performed in all patients before starting anti-TNF therapy.

The median length of follow-up was also defined by the median length of treatment. Duration of response was reflected by the period of time between the first dose (induction phase) and the last dose. Those patients continuing therapy were considered to be in remission by their physicians, so this is a marker of successful maintenance or failure to relapse.

Complete response was defined as remission of the disease: CDAI < 150 points at the last evaluation, partial response is a decrease in CDAI of more than 70 points at 12 weeks after the first administration of ADA/IFX, but remission was not obtained. Non-response is defined as a decrease of CDAI of less than 70 points at 12 weeks after the first administration of ADA/IFX, obviously without remission.

Statistical analysis: Statistical analysis was performed with Minitab statistical software (version 17, Minitab Inc., State College, Pennsylvania, USA). Descriptive statistic was used to summarize the data. Averages with standard deviation were calculated for continuous data and percentages were calculated for categorical data. Demographic and baseline characteristics of the two groups (those who received infliximab and those with adalimumab) were compared using the chi-square test or

Fisher's exact test for categorical variables and the t-Student two-tailed test for continuous variables, which have a normal distribution. P value < 0.05 was considered significant. The association between the demographic, clinical and laboratory parameters and response to therapy were examined through binary logistic regression as we have a dichotomous response variable (response Yes or No).

Results

265 patients were included in the study: 129 on Infliximab (IFX group) and 136 on Adalimumab (ADA group). All these patients are biological naïve. Their demographic and clinical features are showed in Table 1.

Table 1: Demographic and clinical features of patients with Crohn's disease treated with biologicals

| GROUP | | ADA | | IFX | | p-value |
|---|--------------------|---------|--------|---------|--------|--------------|
| | | No. | % | No. | % | |
| No. | TOTAL | 136 | | 129 | | |
| AGE | Mean | 38.154 | | 35.225 | | 0.052 |
| | Std. Dev. | 12.481 | | 11.948 | | |
| SEX | M | 73 | 53.68% | 61 | 47.29% | 0.298 |
| | F | 63 | 46.32% | 68 | 52.71% | |
| INITIAL CDAI | Mean | 260.336 | | 273.855 | | 0.2 |
| | Std. Dev. | 105.31 | | 115.42 | | |
| INITIAL CRP | Mean | 25.858 | | 35.590 | | 0.447 |
| | Std. Dev | 47.668 | | 53.093 | | |
| A subgroups | A1 | 3 | 2.21% | 7 | 5.43% | 0.084 |
| | A2 | 93 | 68.38% | 97 | 75.19% | |
| | A3 | 40 | 29.41% | 25 | 19.38% | |
| L subgroups | L1 | 30 | 22.06% | 14 | 10.85% | 0.013 |
| | L2 | 40 | 29.41% | 56 | 43.41% | |
| | L3 | 66 | 48.53% | 59 | 45.74% | |
| Disease behaviour | B1 | 83 | 61.03% | 67 | 51.94% | 0.001 |
| | B2 | 31 | 22.79% | 18 | 13.95% | |
| | B3 | 22 | 16.18% | 44 | 34.11% | |
| Surgery before biologics | Y | 28 | 20.59% | 23 | 17.83% | 0.569 |
| | N | 108 | 79.41% | 106 | 82.17% | |
| Disease duration (years) | Mean | 3.174 | | 4.129 | | 0.037 |
| | Std.Dev. | 4.106 | | 4.407 | | |
| Azathioprine concomitant with biologics | Y | 112 | 82.35% | 96 | 74.42% | 0.116 |
| | N | 24 | 17.65% | 33 | 25.58% | |
| | Intolerance to AZA | 24 | 17.65% | 19 | 14.73% | 0.632 |
| Corticoreistant /corticodependant | Corticodep. | 118 | 86.76% | 98 | 75.97% | 0.042 |
| | Corticores. | 18 | 13.24% | 29 | 22.48% | |
| | NA | 0 | 0% | 2 | 1.55% | |

According to the data presented in table 1, the two groups of patients are statistically comparable, except for: location (ileal location more frequent in ADA group), disease behaviour (fistulising disease more prevalent in IFX group), disease duration (which is one year longer among IFX treated subjects), corticoreistant cases (more prevalent in IFX group). These data suggest that patients included in the IFX group are more difficult to treat. Regarding all the other parameters, the two

groups are similar: patients are young with a mean of age around 36 years, M:F ratio is about 1:1, with a CDAI mean 270 points (which indicates moderate severity of CD at the moment of biologic initiation) and a CRP mean 30 mg/dl at initiation, approximately three quarters of cases have CD diagnosis between 17-40 years, 20% suffered surgical resections before biologic therapy. The great majority of patients, around 80%, received Azathioprine

before starting IFX/AZA, while rate of intolerance to AZA is quite high, around 15%.

In Table 2 type of response to biologic therapy and therapy duration are presented.

Table 2: Duration of biologic therapy and type of response to therapy according to group of patients

| GROUP | | ADA | | IFX | | p-value |
|-----------------------------------|----------------------------|-------|--------|-------|-------|----------------|
| | | No. | % | No. | % | |
| No. | TOTAL | 136 | | 129 | | |
| Therapy duration (months) | Mean | 19.78 | | 35.78 | | 0.00001 |
| | Std. Dev. | 10.01 | | 19.54 | | |
| Type of response | Complete response | 104 | 76.47% | 84 | 65.1% | 0.96811 |
| | Secondary loss of response | 24 | 17.65% | 37 | 28.7% | |
| | Primary non-response | 5 | 3.68% | 3 | 2.3% | |
| | Partial response | 3 | 2.21% | 2 | 1.55% | |
| Time to loss of response (months) | Mean | 12.71 | | 15.52 | | 0.0734 |
| | Std. Dev. | 9.28 | | 7.87 | | |

Duration of therapy differs significantly between the two groups: patients in IFX group received this drug for approximately 3 years, while those in ADA group for about 1.5 years.

Response to therapy in both groups is comparable and excellent: about 70% of patients respond very well, are in remission, and continue therapy. Secondary loss of response is more frequent among patients treated with Infliximab, about 30%, but that may be explained by the longer duration of the therapy. Risk of non-response is very similar between IFX and ADA, about 3%, while partial response is very rare, about 2% of the patients.

Regarding latent tuberculosis, 52 patients (20.4%) proved to have latent tuberculosis and received chemoprophylaxis with Isoniazid 300 mg per day for 9 months.

6 patients out of 265 (2.26%) were HBs antigen positive and received Entecavir for prophylaxy of chronic hepatitis B reactivation. Only 2 people were diagnosed with chronic hepatitis C (0.7%).

Predictive factors of loss of response to biologic therapy were analyzed: male gender, younger age at diagnosis, perianal disease, fistulising disease, ileocolonic location, azathioprine administration prior anti-TNF therapy, anemia, disease duration, severe disease at initiation. As we can see in Table 3 and Table 4, we failed to identify significant predictors of loss of response to Infliximab respectively Adalimumab.

Table 3: Predictive factors for loss of response to Infliximab

| Predictive factor | Odds ratio (95% CI) | P-value |
|------------------------------|-------------------------|---------|
| Male gender | 1.0200 (0.4879, 2.1324) | 0.958 |
| Younger age at diagnostic | 0.6250 (0.0952, 4.2221) | 0.280 |
| Severe disease at initiation | 1.0021 (0.9988, 1.0054) | 0.216 |
| Fistulising behaviour | 1.1330 (0.5044, 2.5452) | 0.953 |
| Ileocolonic disease | 0.5000 (0.1376, 1.8168) | 0.689 |
| Perianal disease | 0.6389 (0.2332, 1.7506) | 0.372 |
| Azathioprine before anti-TNF | 1.7137 (0.6972, 4.2122) | 0.229 |
| Anemia | 1.8963 (0.8978, 4.0054) | 0.091 |
| Longer disease duration | 1.0441 (0.9585, 1.1373) | 0.326 |

Table 4: Predictive factors for loss of response to Adalimumab

| Predictive factor | Odds ratio (95% CI) | P-value |
|------------------------------|-------------------------|---------|
| Male gender | 0.6365 (0.2788, 1.4530) | 0.282 |
| Fistulising behaviour | 1.8482 (0.6151, 5.5533) | 0.287 |
| Ileocolonic disease | 1.8214 (0.6774, 4.8978) | 0.455 |
| Perianal disease | 1.2667 (0.3761, 4.2661) | 0.707 |
| Azathioprine before anti-TNF | 1.0364 (0.3507, 3.0628) | 0.948 |
| Anemia | 2.1875 (0.9465, 5.0554) | 0.069 |
| Longer disease duration | 0.9990 (0.8967, 1.1129) | 0.985 |

Fig.1 describes the rate of complete response in time for the two groups. There is a tendency towards maintaining a better response in time in

patients treated with Adalimumab, but the p-value was not statistically significant (0.057).

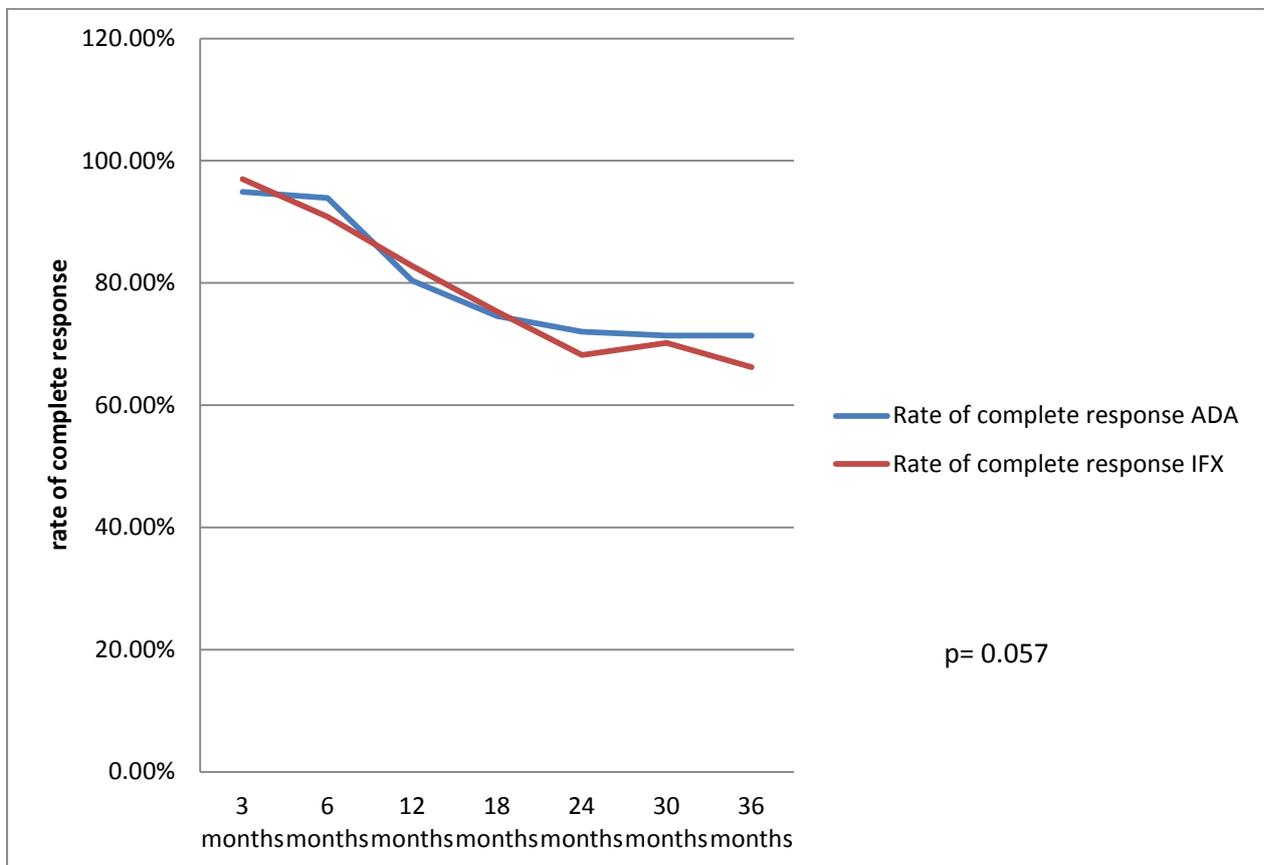


Fig.1: Rate of complete response in time in patients with Crohn's disease treated with Adalimumab/Infliximab

Fig.2 is a flowchart that depicts the evolution of the 136 patients treated with Adalimumab.

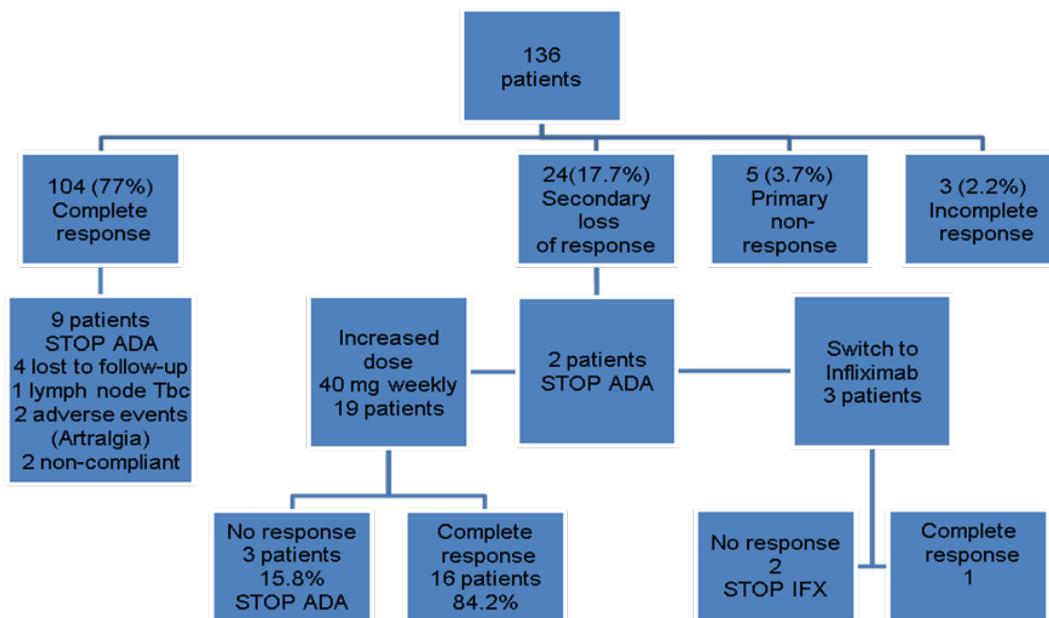


Fig.2: Outcome of patients with Crohn's disease treated with Adalimumab

With most patients with secondary loss of response to Adalimumab (79.2%), the choice was to escalate the dose, which reinduced response in 84.2%. In 12.5% the decision was to switch to Infliximab, but with a significantly lower rate of response of only 33%. 9 patients out of 104 recorded with complete response at

their last check-up stopped Adalimumab, most of them for an unknown reason, one for tuberculous lymphadenitis, 2 were non-compliant and 2 reported adverse events (artralgia).

Fig.3 describes the evolution of the 129 patients treated with Infliximab.

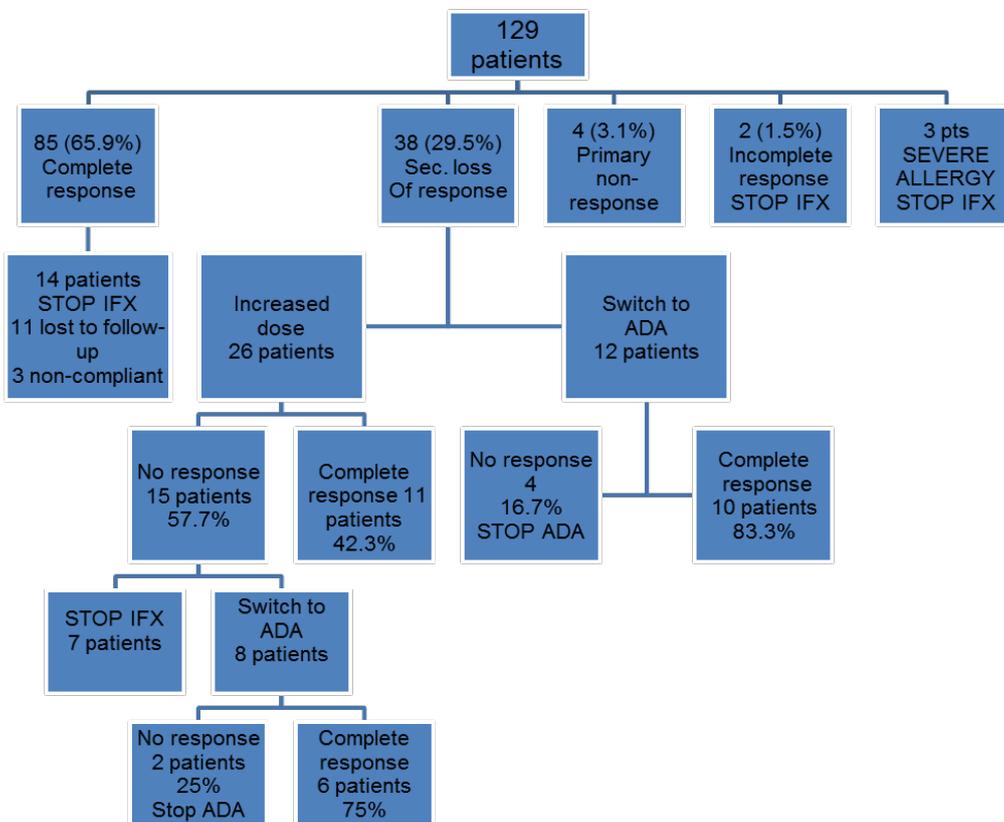


Fig.3: Outcome of patients with Crohn's disease treated with Infliximab.

Out of the 85 patients recorded with complete response on Infliximab, 14 stopped therapy, most of them [11] for unknown reason, while 3 were proven to be non-compliant. In most of the 37 patients that lost response to IFX, the physician decision was to increase the dose, in half of the cases by doubling the dose to 10 mg/kg body weight at 8 weeks, and in half by shortening the infusion interval to 4 or 6 weeks, which resulted in regaining response in approximately 40% of patients. Interestingly, if the physician decided the switch to Adalimumab, which was the case in 12/38 subjects, the result was even better, approx.83% regained response, which happened also in the situation of the 6/8 patients who did not respond to the increased dose of Infliximab.

Regarding safety of biologic therapy: in the Adalimumab group no allergic reaction was reported, we found only one case of erythema at injection site, one patient with lymph nodes tuberculosis, one pustulous psoriasis, one febrile syndrome of unknown origin, 2 patients with artralgiias. In the Infliximab group, 9 cases of allergic reactions were reported (7% prevalence), 3 of them severe, with anaphylaxia, and one case of psoriasis was reported, in a young male, 14 years. 2 deaths were reported in the Infliximab group, none directly related to the drug, one in a patient with severe disease, with no response to IFX, who underwent surgery (intestinal resection), and the cause of death were complications related to surgery. The other death was in a female who associated severe metabolic syndrome and suffered a stroke.

Discussions

Complete response to both biologic agents was comparable (around 70%), and did not differ significantly between Adalimumab and Infliximab. Other authors report the same rate of complete response in cohort study [13]. Secondary loss of response was reported more often in patients treated with Infliximab (almost 30%) than in those who received ADA (approx.17%), but these findings are biased by longer duration of IFX therapy than of ADA therapy. The ACCENT and CHARM trials revealed that secondary loss of response may occur in 20-50% of the patients [5, 14] (e.g., ACCENT I: 28.5%, ACCENT II: 42%, CHARM: 27%).

In the literature only limited data are available on the frequency of dose intensification in ADA treated patients new to biological therapy. Authors report a percentage

of loss of response to ADA among primary responders between 18% and 34% [15, 20, 21, 22, 23, 24]. According to a recent meta-analysis [15], predictors for loss of response or dose escalation were male gender, current/former smoker status, family history of IBD, isolated colonic disease, extra-intestinal manifestations, 80/40 mg induction therapy, longer disease duration, greater baseline CDAI, concomitant corticosteroid use, no deep remission at week 12. Our statistical analysis, performed trough binary logistic regression failed to identify predictors of secondary loss of response to Adalimumab though we studied: severe activity of the disease at the initiation of ADA, perianal manifestations, extension of the disease, fistulising behaviour, concomitant Azathioprine therapy, disease duration, stricturing behaviour, CRP levels. This might be a consequence of a relative small study population (136 patients). Lopez Palacios et al found in their study published in 2008 that perianal fistulising disease has a poor response to Adalimumab [21]. In induction (CLASSIC I) and maintenance (CHARM, EXTEND) adalimumab trials in patients with Crohn's disease, moderate CD patients had the highest clinical remission rate and largest treatment effect size, while moderate-CD/high-CRP patients had the most pronounced efficacy [25].

In case of loss of response to ADA, our study demonstrates that dose escalation is the best option, which is similar to other data from the literature (20)

One of the most important dilemmas in the treatment of IBD nowadays is the efficacy and safety of combined biological and immunosuppressive therapies. Most of the studies report that combined immunosuppressive therapy decrease the frequency of loss of response (9, 15). Some studies found a more favorable response to IFX in combination with immunosuppressant compared to IFX monotherapy [16, 17, 26].

However, in the studies of Kinney et al and Regueiro et al [18, 19], dose intensification was not affected by concomitant use of immunomodulator therapy. In our study, the use of concomitant immunomodulator therapy did not impact on the risk for loss of response to biologicals. This is why we consider that the effect of combined therapy immunosuppressive+biologic is controversial.

Response to IFX in CD patients is excellent in our study: about 65% are in remission at three

years, which is comparable with other data from the literature [26].

We did not find any predictive factors for loss of response to Infliximab though we studied: age at diagnosis, disease activity of the at the moment of starting IFX therapy, perianal manifestations, disease phenotype, and this might be also a consequence of a relative small sample size (129 patients). Other authors suggests that an inflammatory disease phenotype and male gender predicted sustained clinical benefit [26, 27].

Sprakes et al in their cohort study reported that 4.8% patients discontinued infliximab therapy during induction due to intolerable adverse events, a higher proportion than in our study (2.3%). We found indeed a prevalence of allergic reaction of 7%, but two thirds of these reaction were managed by slowing the rate of infusion and anti-allergic therapy. We report 65.1% of 129 patients with sustained clinical benefit compared to 54.3% of the UK cohort study. 28.7% of our patients experienced secondary loss of response, a much higher proportion than in Sprakes study (18.1%), but this difference may be explained by the longer follow-up in our study: 35.8 months versus 17 months. Our patients were managed half with reduction of the interval between the infusions and half with doubling of the IFX dose at 8 weeks, similar with the english study. In our study, patients regained response in 40%, but in the cohort study of Sprakes et al, no patient regained response [26].

One of the most important finding of our study is that patients who experience a secondary loss of response to Infliximab may be more successfully managed with switch to Adalimumab, this strategy leading to regaining response in almost 80% of them. We found no data in the literature for comparison.

If we make a comparison between ADA and IFX in CD, these two biologics are equally effective in Crohn's disease with a sustained long term efficacy rate of about 70%. We have to outline the fact that the two groups of patients are not statistically comparable: the main difference is in therapy duration, which is longer in patients treated with Infliximab (3 years compared to approx.1.5 years in those treated with ADA). Another difference is the disease duration, longer in the IFX group (4.13 years compared to 3.17 years). The percentage of corticoreistant cases is higher in the Infliximab patients (22%), while in ADA group is 13%. Fistulising disease is present in 34% of patients

in the IFX group compared to 16% in the ADA group, while ileal disease is more prevalent in the ADA group (22 vs. 11%). These data suggests that patients that received Infliximab are more difficult to treat.

In the study of Zorzi et al, that also compared ADA and IFX, most of clinical characteristics were similar between patients treated with infliximab vs. adalimumab, but the two study populations differed in terms of CD duration (longer in the adalimumab group), perianal disease (more prevalent in the infliximab group), proportion of corticoreistant patients (higher in the IFX group). Zorzi et al found that Infliximab and adalimumab showed a similar efficacy, and two predictors of steroid-free remission using anti-TNFs were identified: non-smokers and non stricturing non penetrating behaviour [28].

In a very large recently published retrospective cohort study by using U.S. Medicare data from 2006 through 2010, patients with CD were included, who were new users of infliximab (n=1459) or adalimumab (n=871). Some difference between the two groups were found: in the ADA group the 5-th decade of age was predominant, bowel resection was more prevalent in the IFX group (0.8% vs. 0.5%), steroids were more often recently used in the IFX group, but the authors demonstrated good balance among the treatment groups after stratifying on propensity score. The authors observed similar effectiveness of infliximab and adalimumab for CD on the basis of 3 clinically important outcome measures: persistence on therapy, rates of surgery, rates of hospitalization [29].

Another comparative study of Infliximab and Adalimumab in Crohn's disease was performed by Kestens et al in carefully matched cohorts. They found no significant differences between treatment groups: at 1 and 2 years, 62% and 41% of those receiving ADA vs. 65 and 49% of those receiving IFX had responses, respectively. Combining IFX or ADA with immunomodulator therapy was associated with a higher clinical response than monotherapy, but this was only significant among patients who received IFX [30].

59 out of 267 patients suffered resections (ileocolonic or ileal or colonic) before biologic therapy. The indication for surgery was complicated CD, such as small-bowel obstruction or abscess formation due to penetrating disease. 31 received ADA and 28 ADA. 68% achieved complete response,

comparable to non-resected patients (74.5%). 9 of the 28 (32.1) resected patients treated with IFX suffered resection under biological treatment, compared to 4 of the 31 (12.9%) treated with ADA, but p-value was not statistically significant 0.075. 13 of 208 non-resected subjects suffered surgical interventions on biologic therapy (6%).

The strength of our cohort is that it is population-based, because it encompassed all Crohn's patients treated with monoclonals in Romania. An important limitation of this study, inherent to a retrospective study, is the potential underreporting of adverse events, smoking status, and non-uniformity in assessment of some outcome parameters.

In conclusion, the present daily clinical practice series showed that Adalimumab and Infliximab are equally effective in Crohn's disease, with a complete response rate of ~70%. This study failed to identify predictors of poor response to both biologics. In case of secondary loss of response to Adalimumab, the best option seem to be to escalate the dose, which reinduced response in 84.2%, while switching to Infliximab results in a lower rate of response of only 33%. In reverse, patients who lost response to IFX seem to respond better if they were switched to ADA (complete response rate 83%) than if their dosage was increased (response in 42%).

Abbreviations

CD- Crohn's disease
 CDAI- Crohn's disease activity index
 IFX- Infliximab
 mAb- monoclonal antibody
 ADA- Adalimumab
 TNF- Tumor necrosis factor
 AST- Aspartate Aminotransferase
 ALT- Alanine Aminotransferase
 CRP- C reactive protein
 AZA- Azathioprine
 OR- Odds ratio

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patients. Negreanu Lucian treated studied patients. Constantinescu Gabriel treated studied patients. Becheanu Gabriel performed statistical analyses and contributed by critical revision of the manuscript. Manuc Mircea treated studied patients. Cijevschi-Prelipcean Cristina treated studied patients. Iacob Razvan treated studied patients. Tieranu Cristian treated studied patients. Meianu Corina performed statistical analyses and contributed by critical revision of the manuscript. Diculescu M designed the study, treated studied patients and contributed by critical revision of the manuscript. All authors read and approved the final manuscript.

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Informed consent statement: All subjects included signed an informed consent stating that their data can be used in scientific purposes

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