Infliximab therapy for Crohn’s disease anoperineal lesions

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SUMMARY

Infliximab (Remicade®) has been shown to be an efficacious treatment for fistulae in patients with Crohn’s disease, but its long term efficacy remains uncertain.

Aim of the study — To retrospectively evaluate the efficacy, the duration of response, and the tolerance of Remicade® in anoperineal Crohn’s disease.

Methods — Fifty patients with severe symptomatic and refractory anoperineal Crohn’s lesions (38 fistulae and 29 cavitating ulcers and superficial fissures) were treated with 3 intravenous infusions of Remicade® (5 mg/kg) at weeks 0, 2 and 6. Efficacy was assessed using Allan’s functional score and proctologic examination at 8 weeks (W8) and 24 weeks (W24) after the first infusion.

Results — At W8, a response was noted for 71% (27/38) of fistulae and 79% (23/29) of ulcers and fissures. Healing rates were 39% and 49%, respectively. Efficacy of Remicade® at W8 did not vary according to sex, number and type of fistulae and other treatments. At W24, 58% (15/26) of patients with fistulae and 63% (10/16) of patients with ulcers or fissures had a response. The response rate at W24 was higher in patients having anoperineal Crohn’s lesions for less than one year: 77% vs 32% (P = 0.004). Median Allan’s score significantly decreased from 3.9 before treatment to 1.7 at W2 (P < 0.001), 1.3 at W6 and 0.8 at W8. Median duration of response was 9.5 months (range: 0.5-12.5) after last infusion and was not influenced by associated treatments including immunomodulators. The relapse rate at 1 year was 64% for the responders followed at least one year (n = 21). Minor adverse events occurred during 12% of all infusions. Eight patients had an infection, including one pneumonia. Eight patients developed a perineal abscess 16 weeks (range: 4-32) after the first infusion.

Conclusion — Remicade® is rapidly effective and well tolerated in anoperineal Crohn’s lesions, but the high relapse rate stresses the need for long term therapeutic strategies in these patients.

Key words: Crohn’s disease. Anoperineal lesions. Infliximab.


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proximately one half of patients with Crohn’s disease (CD) develop perianal lesions, particularly when the disease involves the distal portion of the digestive tract [1]. Generally chronic and relapsing, perianal Crohn’s disease (PACD) may affect continence and genital function, greatly deteriorating quality of life. Medico-surgical care is difficult [1]. The goal of treatment is symptom relief and improved quality of life in an attempt to cure the lesions, prevent relapse, and reduce the risk of sphincter destruction and the subsequent need for proctectomy [2]. Since the recent publication of the first controlled trial using anti-TNF α chimeric antibodies (infliximab, Remicade®) for the treatment of perianal and enterocutaneous fistulae showing complete closure in 31% of the patients after 3 perfusions of Remicade® versus 6% in the placebo group [3], has changed attitudes in these difficult-to-

manage problem current treatment protocols should be revisited. The efficacy of this new treatment for perianal ulcerations has not however been assessed and long-term outcome after Remicade® treatment remains largely unknown.

The purpose of this work was to assess the short- and long-term efficacy of Remicade® and tolerance to treatment in patients with severe PACD.

Patients and methods

Patients

This open, multicentric study was conducted between February 1999 and August 2000 in 50 patients with severe refractory PACD treated with Remicade®. Prior to the official marketing approval for Remicade®, the French Drug Agency authorized temporary use in 39 patients. After official approval awarded in January 2000, Remicade® was given to 6
other patients within the marketing approval specifications and to 5 others outside the marketing approval specifications. In this retrospective study, criteria for severity of PACD, the refractory nature of the disease, and the decision to treat were determined independently by each attending clinician. The patients were treated in seven different centers (Lille, n = 31; Nancy, n = 8; Paris-Saint-Louis, n = 5; Paris – Rothschild, n = 5; Marseilles, n = 2; Lyon, n = 1; Lourdes, n = 1). There were 14 men and 36 women, median age 31 years (age range, 17–69 years) who had Crohn’s disease for a median 7 years (range, 1–62 years). All the patients had perineal fistulae alone (n = 20, 38%), perineal ulcerations alone (n = 12, 23%) or both (n = 13, 29%). There were 3 enterocutaneous fistulae and 2 perianal fistulae in two patients who also had perianal ulcerations. The perianal involvement had persisted for a median 15.5 months (range 1-168 months). The perineal fistulae (n = 35) were unique in 27 patients (77%), and multiple in 8 (23%), situated low in 76 (74%) and high in 9 (26%). There were 3 anovaginal fistulae. APACD at week 1, According to the Cardiff classification [4], PACD was grade S0 (is given in table I). Associated intestinal involvement concerned the ileum in 6% of the patients, the colon in 44%, and both in 50%. Surgical resection for CD had been performed in 55% of the patients and 32% had recently undergone surgical treatment: drainage (n = 12), flap (n = 1), fistulotomy (n = 3). The patients were taking one or several medical treatments concomitantly: corticosteroids (n = 8, 16%), azathioprine (AZA) or 6-mercaptopurine (6MP) (n = 33, 66% for a median duration of 20 months, range 1-120 months), metotrexate (n = 6, 12%), methotrexate (n = 5, 10%), mycophenolate (n = 1, 2%), aminosalicylates (n = 4, 8%), or antibiotics (metronizazole or ciprofloxacin) (n = 7, 14%). Five patients (10%) had no medical treatment. Thirteen of the 50 patients had interrupted prior AZA therapy because of treatment failure in 5, immunological pancreatitis in 4, and intolerance in 4.

The patients were given 3 intravenous perfusions of 5 mg/kg Remicade® over 2 hours at weeks 0, 2 and 6 (w0, w2, w6).

Efficacy of the Remicade® infusion

Outcome was assessed on the basis of the proctology findings at week 8 and week 24 (w8, w24) compared with w0. Secondary outcome criteria were function as assessed by the Allan score [5] and magnetic resonance imaging of the perineal area. The Allan score includes 7 clinical parameters which the patient scores on a 0 to 10 on a visual analogue scale: perineal pruritis, spontaneous anal pain, pain following defecation, anal oozing, inhibition of locomotion by pain, inhibition of social life, inhibition of sexual activity. The Allan system gives a mean score where the sum of the scores for each clinical parameter is divided by the number of parameters studied, each having the same weight. A proctology examination was performed at w0, w8, and w24. Outcome was scored 0 for no improvement, 1 for minor improvement, 2 for major improvement, and 3 for cure. Fistulae with persistent purulent retention were scored 0, those which were productive but without purulent retention were scored 1, those where which were no longer productive but with an open oriifice and/or closure of more than 50% of multiple orifices were scored 2, and those that had closed were scored 3. For perineal ulcerations, the size and depth of the ulceration was scored 0 to 3. Response to Remicade® at w8 and w24 was defined as a clear improvement (score = 2), or healing (score = 3) compared with w0. Allan’s functional score was recorded for 30/50 patients at w0, w2, w6, and w8.

MRI of the perineal region was performed in 18 patients (all in one center, Lille) at w0 and w8 on a 1 Tesla Expert machine (Siemens) with T1 and T2-weighted fat-suppression axial and frontal sequences. All images were read by one radiologist (OE) who was blinded to the clinical outcome. Change in morphology of fistulae and ulcerations (before versus after treatment) was scored 0 to 3 (0 = no change in size, 1 = less than 50% reduction in size, 2 = more than 50% reduction in size, 3 = image no longer visible). Response was positive when the MRI evaluation was scored 2 or 3 at w8 and w24 compared with w0.

Remission was defined as the absence of relapse during the follow-up after initial positive response observed at the proctology examination.

Adverse effects of Remicade® treatment

Patients were examined and monitored (pulse, blood pressure, temperature) at each infusion (w0, w2, w6) and examined at each visit (w8, w24) to search for adverse effects. Intolerance to the perfusion, defined as any adverse effect observed during infusion or within the two hours following the end of the infusion, were distinguished from adverse effects observed between infusions or several months later.

Blood tests performed at w0, w8, and w24 included: blood cell counts (BCC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function tests, blood chemistry, urea, creatinine, and viral serology (HIV, hepatitis C Band BC, herpes, cytomegalovirus, Epstein-Barr) and antinuclear antibodies; at w2 and w6: BBC, ESR, CRP, liver function tests, blood chemistry, urea, creatinine. Indirect immunofluorescence using on the HEP2 line was used to search for antinuclear antibodies: greater than 1/80 was considered positive. If positive, immunofluorescence ELISA for anti-native DNA antibodies (> 100 IU/ml positive) and the Farr test (> 7 IU = positive) were performed.

Statistical analysis

Quantitative data were expressed as median and range.
Fisher exact test or chi square, as appropriate, were used to compare qualitative variables between groups. Wilcoxon test for independent variables was used to compare quantitative data due to the small sample size ($n < 30$). Student’s $t$ test for paired variables was used to compare Allan scores at w0 and w2 ($n = 30$). Kaplan-Meier curves were plotted and compared between patients with or without AZA/-MP treatment using the log rank test. Concordance between proctology findings and MRI findings were compared with the simple Kappa test. Differences were considered significant for $P < 0.05$.

## Results

### Proctology examination

A positive response was observed at w8 for in 71% of patients with fistulae (27/38), including 39% (15/38) which healed (figures 1a, 2a, and 2b). The corresponding percentages were 79% (23/29) and 48% (14/29) for ulcerations (figures 1c, 2c, and 2d). There was no significant difference in response by sex, duration of PACD, or concomitant medical treatment. Response was observed for 7 of the 8 multiple fistulae, and 17 of the 27 unique fistulae (NS) and for 16 of the 26 low fistulae and 8 of the 9 high fistulae (NS). Three patients had ano-vaginal fistulae. Complete closure was observed in one patient at w8 followed by relapse at w16; the 2 other patients did not respond to treatment. The three enterocutaneous fistulae were had closed at w8 with 1 relapsed at w16. Response was observed in 1 of the 2 peristomial fistulae at w8. One patient with ulcers on the genital organs and in the intergluteal groove achieved clear improvement at w8 (score 2) and minor improvement at w24 (score 1).

A response was observed at w24, a response was observed for in 58% of patients with fistulae (15/26), including 31% (8/26) which healed (figure 1b). The corresponding percentages were 63% (10/16) and 50% (8/16) for ulcerations (figure 1d). There was no significant difference in response by sex, low or high fistulae, number of fistulae, or concomitant medical treatment did not influence results. Patients whose PACD was recent (less than 12 months) exhibited a significantly better response at w24 than those with longstanding PACD (> 12 months): 77% versus 32% ($P = 0.04$).

### Functional assessment

Symptoms improved in all patients, even those classed as non-responders at the proctology examination. There was a rapid decline in the Allan score after the first infusion (figure 3) that was maintained at w6 and w8. Median Allan score was 3.9 at w0 (range, 1-10), 1.7 at w2 (range, 0-8.8) ($P < 0.001$), 1.3 at w6 (range, 0-4.4), and 0.8 at w8 (range, 0-4.8). Median score tended to increase again at w24 but only 13 patients were assessed at this time.
MRI morphological assessment

Response was observed at w8 in 45% of patients with fistulae (5/11), with complete healing in 0% (figures 4a, 5a, and 5b). The corresponding percentages were 71% (5/7) and 43% (3/7) for ulcerations (figures 4b, 5c and 5d). Response rate was lower as assessed by MRI than as assessed by the compared to proctology examination, both for fistulae (45% versus 82%) and for ulcerations (71% versus 86%). Four patients with fistulae who were classified as responders at the proctology examination were classified as non-responders on the basis of the MRI findings. These 4 patients experienced relapse at w16 (4 months). MRI and proctology results were not correlated (P = 0.13).

Mid-term Follow-up evaluation at Mid-term course

The median duration of follow-up was 9.5 months (range, 2-18). Among the 39 responders at w8, 32 were followed for at least 6 months after the first infusion and 21 were followed at least one year: remission rate = 78% at 4 months (n = 36), 65% at 6 months (n = 32), 51% at 10 months (n = 24), and 36% at 12 months (n = 21). Thus 64% of the patients experienced a relapse 1 year after treatment onset. Median duration of remission among patients followed at least 1 year was 11 months (range, 2-14). There was no significant difference between duration of remission among patients with or without AZA/6MP treatment. Median duration of remission among patients without not treated with AZA/6MP treatment was 10 months, and could not be estimated among those treated with AZA/6MP treatment because 50% of the population had relapsed at 1 year.

Sixteen of the 39 responders at w8 were found to have relapsed at (proctology examination): 6 were retreated with Remicade®, 3 underwent surgery for derivation of the fecal flow (1 after failure of second treatment attempt), 1 had flap surgery, 2 had long-term derivation, 3 underwent proctectomy (1 after failure of second treatment attempt), 1 was given thalidomide, and 2 were not given complementary treatment. Eleven patients were non-responders at w8: 3 were retreated for functional relapse, 2 had a surgical flap, 1 had drainage, 1 a derivation of fecal flow with stomycolostomy, and 4 were not given complementary treatment. In all, 10 patients out of 50 were given secondary treatment with Remicade®: 6 for relapse (proctology examination) after an initial response to the first perfusion cycle, 4 for functional relapse (including 3 who did not respond to the first infusion cycle). Two of the 3 non-responders to initial treatment responded to the second treatment. Among the 5 responders to the initial treatment who could be evaluated, 1 responded to the second treatment.

Fig. 2 – Perineal fistula before (a) and after (b, W8) Remicade® administration: healing (score = 3). Perineal ulceration before (c) and after (d, W8) Remicade® administration: clear improvement (score = 2).

Fig. 3 – Evolution of Allan’s score (median) during treatment with Remicade® in 30 patients.

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given concomitant corticosteroid therapy and 6 had a history of a preceding perineal abscess.

Ten of the 50 patients (20%) were positive for antinuclear antibodies at w8: 3 had a low titer before initiating Remicade® treatment. None of the patients developed signs of lupus and anti-native DNA antibodies and the Farr test were negative in all. There were no deaths during the study period. No malignant disease or intestinal obstruction of the intestine was observed.

### Discussion

The results of this study confirm the short-term efficacy of Remicade® for the treatment of fistulous Crohn’s disease fistulae. The response and cure rates were comparable with the 68% rate of 50% reduction in draining fistulae and 31% rate of complete closures after 3 infusions reported by Present et al. [3]. These authors also demonstrated for the first time that Remicade® provides equally efficacious treatment for fistulae and ulcerations in patients with PACD. Functional improvement, as assessed by the Allan score, was observed in all patients, even those classed considered as “non-responders” at the proctology examination. Functional improvement was achieved within 15 days of the first infusion and was maintained thereafter. In this series, we did not identify factors predictive of short-term response to Remicade®. Response and cure rates were similar, irrespective of the number, the duration or the type of the fistulae, much like in similar to the series by Present et al. [3]. The efficacy of Remicade® was observed in a few particular clinical situations only rarely reported [6]: severe perineal degradation with ulcerations on the genital organs and in the intergluteal groove, and peristomal ulcerations.

One of the major problems with using Remicade® in PACD is lack of long-term efficacy. Sixty-four percent of our patients relapsed within 1 year after treatment onset. This is similar to earlier reports. d’Haens et al [7] had 40% and 90% relapse rates among 20 patients with fistulae, 4 months and 1 year after the last infusion, respectively. Toy et al. [8] reported that one-third of their 38 patients relapsed 2 months after the last infusion. Patients who relapse also appear to respond less well to future Remicade® infusions: among the 5 patients in the present series who responded to the initial treatment, only 1 responded favorably to retreatment. The rate of relapse was not different for the number or type of perineal lesion. Conversely, patients with longstanding PACD (more than 12 months) relapsed more often than those with recent disease. Certain authors [9], but not others [3, 7] suggested that combining Remicade® infusion with AZA/6MP could prolong fistular response to Remicade® in treating fistulae. In our experience, the median duration of remission was not influenced by concomitant immunosuppression, particularly when using efficacious doses of AZA or 6MP doses and for a median duration of 20 months (range, 1-120 months).

We were able to compare proctology and MRI findings at w8 after Remicade® in a subgroup of patients. The two evaluation methods were not correlated, but the sensitivity of MRI for evaluating perianal ulcerations is not known. The response rate was lower according to the MRI assessment compared with proctology assessment, both for fistulae and for ulcerations. MRI did not visualize complete resolution of the any fistulous tracts. In 4 patients with fistulae, MRI did not demonstrate any response while the proctology examination did. These 4 fistulae relapsed at w16 (4 months). Thus persistent fistulae visible on the MRI, but not at the proctology examination, might be predictive of relapse after Remicade® treatment. This has already been reported for multiple entero-cutaneous fistulae [10].

Twelve percent of the infusions produced intolerance reactions. These were minor adverse effects (excepting the two cases of intolerance were observed during 12% of the first infusions, 10% of the second infusions, and 6% of the third infusions. Among the 27 retreatment infusions in 10 patients, 2 (7.4%) triggered a severe anaphylactic reaction with skin rash, facial edema, dyspnea, and in 1 case hypotension. All responded to antihistamine and corticosteroid treatment after interruption of the Remicade® perfusion. In all, 4 of the 177 perfusions (2.3%) were discontinued, 2 definitively. Two infusions were reinitiated at a slower rate after intravenous administration of corticosteroids or antihistamines.

Eight patients developed 11 minor infections, including 1 lung infection/pneumonia 15 days after the first infusion that resolved after ambulatory oral antibiotic therapy (table III). Eight of the 50 patients (16%) developed a perineal abscess 16 weeks after the first infusion (range, 4-32 weeks); all resolved with antibiotics, incision or curettage, then drainage. Three of these 8 patients did not have an MRI prior to the first infusion. Three were

### Adverse effects of Remicade®

Adverse effects of the Remicade® treatment were observed in 22/50 patients (44%). Intolerance was noted during 22 of the 177 infusions (12.4%), including 27 retreatment infusions (table II). The most frequent clinical manifestations were headache that resolved in less than 48 hours (n = 8, 4.5% of all 177 infusions), and skin rash (n = 4, 2.3% of all infusions). Signs of intolerance were observed during 12% of the first infusions, 10% of the second infusions, and 6% of the third infusions. Among the 27 retreatment infusions in 10 patients, 2 (7.4%) triggered a severe anaphylactic reaction with skin rash, facial edema, dyspnea, and in 1 case hypotension. All responded to antihistamine and corticosteroid treatment after interruption of the Remicade® perfusion. In all, 4 of the 177 perfusions (2.3%) were discontinued, 2 definitively. Two infusions were reinitiated at a slower rate after intravenous administration of corticosteroids or antihistamines.
of severe anaphylactic reaction during retreatment infusions). The patients who developed an adverse reaction to the infusion did not necessarily develop reactions during the subsequent infusions. This is in agreement with published data in the literature where intolerance to Remicade® infusion was 16% in patients with CD compared with 10% in the placebo group [11]. Twelve percent of the first infusions, 10% of the second infusions and 6% of the third infusions produced adverse effects. Only 4 infusions were discontinued, 2 being reinitiated later at a slower infusion rate. Seven percent of the retreatment infusions produced adverse effects. This frequency is no greater than that observed for the initial infusions but the reactions were more severe. Two of these 27 retreatment infusions had to be definitively interrupted due to severe anaphylactic reactions. Like others, we did not have any reactions suggestive of serum sickness. In the initial trials, 9% of the patients treated with Remicade® (CD and rheumatoid arthritis) developed anti-native DNA antibodies or anti-double stranded antibodies, with 3% of the patients retaining long-term

Table II. Acute infusion reactions observed in 50 patients treated with Remicade®.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>First infusion</th>
<th>Second infusion</th>
<th>Third infusion</th>
<th>All infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Skin rash</td>
<td>1</td>
<td>1 + 2*</td>
<td>0</td>
<td>2 + 2*</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0</td>
<td>1*</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>2*</td>
<td>0</td>
<td>2*</td>
</tr>
<tr>
<td>Hypotension</td>
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<td>1*</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>Facial edema</td>
<td>0</td>
<td>2*</td>
<td>0</td>
<td>2*</td>
</tr>
</tbody>
</table>

Total 6/50 12 % of the infusions 5/50 10 % of the infusions Excepting retreatments 3/50 6 % of the infusions (9.3 %) Except in retreatments 14/150 9.3 % of the infusions excepting retreatments 22/177 (12.4 %) of the infusions including retreatments

* At retreatment.

Fig. 5 – MRI examination. Perineal fistula before (a) and after (b, S8) Remicade® administration: the size of the fistula (arrow) is reduced by a > 2 ratio (score = 2). Perineal ulceration before (c) and after (d, S8) Remicade® administration: complete disappearance of the ulceration (arrow) (score = 3).
positive titers [11]. For Present et al. [3] reported a, 13% of the patients were positive rate. Three resolutive lupus syndromes which resolved with corticosteroids have been reported in the literature [12]: 2 in rheumatoid arthritis patients and 1 in a CD patient with manifestations of arthritis [12]. Anti-nuclear antibodies were positive in 20% of our patients at w8, but none of the patients were positive for native DNA antibodies or on Farr test. Production of anti-nature DNA antibodies would be less frequent in patients taking immunosuppressors [11]. In our series, 78% of the patients taking AZA/6MP or methotrexate were positive, compared with 39% in the series reported by Present et al. [3].

Eight patients developed minor infections. Systematic clinical and serological monitoring did not reveal any opportunistic infections at w8 or w24. In the controlled trials in CD and rheumatoid arthritis patients, overall rate of serious infection requiring hospitalization was not greater in patients given Remicade® (2.4% versus 1.8% for placebo). Eight patients developed a perianal abscess between 4 and 32 weeks after the first infusion, although certain pre-existing abscesses may have been missed at the initial proctologic examination. Three of these 8 patients did not have an MRI before initiating the infusions. Our results suggest that concomitant corticosteroid treatment (3/8 patients) and antecedent a past history of perianal abscess (6/8 patients) are risk factors for the development of abscesses; this however, merits further study.

We did not have any malignant complications in our 50 patients. To date, 2 cases of lymphoma have been reported among CD patients treated with Remicade® [13]. This is not greater than that observed during the spontaneous course of the disease. Prolonged surveillance is however necessary.

In conclusion, our findings confirm that Remicade® is a rapidly efficacious and well tolerated treatment for perianal Crohn’s disease. The high rate of relapse implies the need for longer term therapeutic strategies; current protocols being tested include repeat infusions and/or therapeutic combinations.

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