

THERAPY

Immunosuppressive treatment of Crohn's disease with fistulae

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*Department of Internal Medicine, Gastroenterology University, Hospital Bohunice, Brno, Czech Republic. pdite@med.muni.cz***Abstract**

The rise of fistulae in Crohn's disease has been classed with the disorder complications, although it is a possible component of natural development of the so-called A type (De Dombal classification) or aggressive-perforating type (Greenstein's classification) of this idiopathic intestinal inflammation. Fistulae are accompanying colic localization of Crohn's disease in 20 %, ileocolic affection in 40 %, where 35 % of them are perianal fistulae, and about 34 % entero-enteral or entero-cutaneous ones. Other complications (urogenital tract, biliary tract) are mentioned unfrequently in literature. Besides surgical approaches in the therapy, dominant post in the conservative area is taken up by an anti-tumor necrotizing factor, antibiotics and immunosuppressives whose position is, however, the most problematic although the literature references about the effectiveness of azathioprine, 6-mercaptopurine, cyclosporine, takrolime and methotrexate have had nearly 25-years tradition. The authors present their own experience with applying a combination of cyclosporine, azathioprine in the treatment of perianal fistulae in a set of 21 patients from the period of 1995—2000. In their opinion, the therapy success is limited especially by early starting the treatment (11 cases of effective therapy) and choosing a resolute method that is, according to them, sequential immunosuppression. (*Tab. 2, Ref. 32.*)

Key words: IBD, inflammatory bowel disease, Crohn's disease, CyA, cyclosporine A.

The rise of fistulae in CD has been traditionally classed with complications (1, 2) although it is a component of the natural disorder development. The presence of fistulae belongs to the clinical picture of the so-called type A classification according to De Dombal from 1971 (3), or the so-called aggressive-perforating type of CD according to Greenstein's classification (4). Whichever classifications (this one or any other) is used, it is clear that the presence of fistulae in CD patients in only one of tips of the iceberg formed by the therapy for CD from establishing the diagnosis, the treatment of fistulae and prevention of relapses and recurrences up to successful conservative or surgical treatment.

Most authors have stressed that the disease development in the first year of duration often anticipates the prognosis for years or even decades forward (3, 5, 6). In the primary location of CD, there exist the greatest differences in the data concerning the perianal localization, which results from the choice of evaluating criteria. Rankin (7) and Fielding (8) have come to 12—14 % occurrence of this location. Rankin has presented the results of National Crohn's Cooperative Disease Study from the prospective follow-up of 569 patients in whom fistulae, fissures and the

development of abscesses were assessed as manifestations of perianal affection. Mařatka's set of 303 patients (9) from 1993 showed 27 % affections of the small intestine, 20 % of the large intestine, 45 % of both bowels simultaneously, 3 % of perianal locations, and 5 % of other involvement. According to Munkholm (10), further unfavourable development of aggressive-perforating type of CD can be modified by early intensive treatment with corticosteroids in a descending dosing scheme as early as its first attack. Less than 20 % remission is reached without the corticosteroid application, and 44 % after their use, which is, however, connected with manifestations of corticosteroid dependence (36 %) and corticoreistance (20 %) in the further course of the disease in the 2nd—5th years of its duration. The patients who are without response to the corticosteroid treatment in the

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first attack of therapy, or in further course they have the mentioned features of steroid dependence thus become natural candidates of immunosuppressive therapy. So it is possible that as many as 50 % of patients with aggressive-perforating CD type have been already treated with immunosuppressive in the moment of the fistula rise.

From the view of therapeutical approaches to fistulae in CD, the risk of their development and location must be known. Farmer (11), McDaniel (12), and Pichney (13) have given the following percentage of the fistulae rise:

- 20 % in a purely colic form of CD,
- 40 % in ileocolic involvement,

— the incidence of fistulae in CD locations in the esophagus, stomach and duodenum was described only in 27 cases in 1995.

Another important data for the therapeutic application is the fistula type with respect to its localization:

— perianal fistulae accompany about 35 % cases of ileal and colic location of CD. Gabriel (14) described these fistulae as early as 10 years before the classical description of CD. Fistulae together with anal stenosis, anal fissures and abscesses are manifestations of the so-called perianal CD (15), although, due to conspicuously high percentage of incidence, even internal hemorrhoids and dermal fibrous changes near the anus are also reckoned with them by some authors.

— Entero-cutaneous and entero-enteral fistulae occur in the ileocolic location of CD in 34 %, in the colic location in 16 %, and in the CD location in the small intestine in 17 %. Other orifices (urogenital tract, biliary tract) are mentioned infrequently in literature.

From the view of the therapy of treatment for fistulae in CD, some authors have shown that the results of treatment are influenced by the speed of starting energetic therapy (16). According to most current authors, the perianal localization of CD is an indication for initiating the therapy with corticosteroids, e.g. Lukáš (17) has mentioned it directly among five other indications, Lofberg (18) has done in with certain exceptions and he considers this CD location a relative indication. But he has recommended to apply the steroid therapy in fistulae. Korelitz (19) is of the same opinion — he has reported the healing of fistulae after the immediate treatment application. However, positive effects of energetic corticosteroid therapy on the perianal inflammatory infiltrate and longer-lasting fistulation with chronic features must be strictly differentiated. While in the former case certain effects can be expected, in the latter — there has been even demonstrated the deterioration after the steroid treatment when false and temporary healing is associated with a persistent mycotic focus, the so-called mycotic aneurysm (20) that is a source of extensive relapses controllable with difficulties in every fifth patient.

Azathioprine, *6-mercaptopurine* was applied by Korelitz (21) in 1985. He reported on 50 % responsibility of perianal fistulae after applying the dose of at least 2 mg/kg/day. The therapeutic effects appeared in the course of about 3 months. In a set of 44 adolescents, Markowitz (22) healed perianal fistulae by means

of 6-mercaptopurine in 44 %, without its application in 14 % only. Similar experience has been given by Jeshion (23) and Hibi (24) who, moreover, registered quite minimal side-effects of longer-lasting therapy.

The undoubted advantage of *cyclosporine A* is the fast onset of effects, which enables the early evaluation of the therapy efficacy, by means of which the potential toxicity of this therapy as well as the probable rise of spontaneous remission mis-attributed to the therapy effect decrease. In 1994 Present and Lichtinger (25) reported on a set of 16 patients with perianal fistulae in whom two-week's therapy with intravenous CyA in the dose 4 mg/kg/day at maintaining cyclosporinemia about 500—700 ng/ml caused a significant improvement up to the fistula disappearance. Hanauer et al (26) reached the complete healing of perianal fistulae in three patients after the oral administration of CyA, but remissions appeared by 3 weeks up to 7 months after terminating the therapy. Most new reports (27) have concluded that CyA must be applied in the initial dose of at least 7 mg/kg/day optimally in the parenteral form, and then the oral doses of at least 4—5 mg/kg/day should continue. Our own published experience with the use of CyA (28) has been similar.

FK 506 — tacrolimus has been applied in the treatment of fistulae in CD only recently either in monotherapy (29) or in combinations (30).

Methotrexate is considered an immunosuppressive agent with significant effects on fistulae, particularly in the age group up to 40 years with the perianal location of the aggressive CD form (31, 32). The recommended dose is 20—25 mg once a week applied parenterally.

Set and Methods

Within the period of 1995—2000 totally 37 patients with fistulae in aggressive-perforating type of CD, out of them 25 with perianal location, were treated in our workplace. In a set of four patients, there was used methotrexate, it was not involved in the set studied.

21 patients suffered from one to five perianal fistulae with the presence of secretion, the mean time of duration 18 months. The longest registered presence of fistulation was 36 months, the shortest 10 weeks. No rectovaginal, rectovesical, entero-enteral or entero-cutaneous fistulae were observed. The set consisted of 9 women and 12 men, mean age 28.4 years. A set survey is given in Table 1.

Fistulography was carried out in all the cases, and fistulae communicating with the rectum were demonstrated in 17 patients.

Tab. 1. A set of CD patients with perianal fistulae (1995—2000).

Set	Patients	Communicating fistula	Non-communicating fistula	Mean age (years)
Men	12	11	1	25,6
Women	9	6	3	31,2
Total	21	17	4	28,4

Tab. 2. Results of sequential immunosuppression.

Set	Patients number	Time of fistula healing					
		Week 0	Week 4	Week 12	Month 6	Month 9	Month 12
Men	12	0	4	6	6	5	4
Women	9	0	3	5	5	5	5
Total	21	0	5	11	11	10	9

11 patients underwent computer tomography of the small pelvis, and two of them were examined by supplementary nuclear magnetic resonance of the same localization.

In the time of starting the therapy, all the patients were treated with mesalazine in the dose of 2–3 g/day, and with prednisone in the daily dose of 7.5 mg–20.0 mg. In the course of therapy, no antibiotics from the CD indication, anticytokines were applied, the doses of corticosteroid therapy were not changed.

The therapeutic scheme was as follows:

1. The 1st–12th weeks CyA preparation Consupren tbl. Made by IVAX 25, 50, 100 mg. In weeks 1 and 2 — daily dose of 8 mg/kg, then reduced by 1 mg/day after one week to the lowest dose of 5 mg/kg/day. The treatment was terminated in the 13th week.

2. Azathioprine since week 2 in the daily dose of 2.5 mg/kg. If the efficacy was presumed, the therapy was extended to one year, when the fistulae was not healed, the treatment was terminated after four months.

The evaluating scheme was as follows:

1. external secretion from the fistulae — weeks 2, 4, 12 and then months 6, 9, and 12;

2. fistulography when the external orifice of the fistula was evident — months 3, 6, and 12;

3. CDAI was a part of evaluation — months 3, 6, and 12.

Results

Out of 21 patients treated, 11 cases demonstrated significant improvement characterized by stopping secretion from fistulae, and by closing the external orifice in the average period of 8 weeks of therapy (Tab. 2). No control fistulography could be realized in these patients, CDAI decreased from the average value of 186 points before therapy to 94 after terminating the treatment with CyA. After going on monotherapy with azathioprine, the fistula recurrence was seen in two patients only, namely in the 8th and 10th months of treatment. Fistulation did not re-develop in the other 9 patients even one year later. No significant decrease of secretion from fistulae occurred in a set of 10 patients, control fistulography showed unchanged conditions, as well as the CDAI fluctuations were insignificant.

Discussion

The result analysis was focused on the differences in the sets of responding and non-responding patients. Neither significant

differences of the age average (27.2 years in the group with effective therapy, 29.0 in the group not responding to treatment) nor the ratio of both sexes representation were found out. The only essential difference could be seen in the time of registering the fistula presence. While in the first group responding favourable to the immunosuppression chosen perianal fistulae were present, on the average, for about 6 months, in the group not responding to treatment this period was about 30 months. That fact correlates with the conclusion that the older fistula, the worse response to any type of conservative therapy (16). This could explain conspicuous disagreement concerning the effectivity of immunosuppressive agents in this indication (20, 21, 22, 25, 27, 28). Based on a retrospective analysis of available documentation, previous therapeutic response: insufficient utilization of classical steroid treatment, short-term and low-dose therapy with azathioprine or methotrexate were found out in a number of patients. Due to the available documentation, these conclusions are hypothetical.

The fistula relapse in two patients, out of the 11 healed (3.8 %) has been considered successful. In our opinion, it was caused by exchanging CyA for azathioprine because only this can explain that the discontinuation of CyA was not accompanied by the expected number of recurrences (26). This also suggests a variant for possible prophylaxis that should be verified in further investigation.

The authors have used sequential immunosuppression by means of CyA-azathioprine with 52.4 % relative success in patients with perianal fistulae in aggressive-perforating type of CD. 12-week's CyA therapy was followed by one-year azathioprine treatment in the course of which the fistula relapse occurred in two cases only (3.8 %). Although the success of immunosuppression in the therapy for fistulae was not greater than that given in literature, the number of recurrences can be decreased substantially by the sequential combination mentioned (literature gives 60 % by six months after terminating the CyA treatment). In the authors opinion, the therapeutic success is significantly higher if a fistula does not exist for more than 8 months on the average. Then the probability of efficacy decreases steeply.

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