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Individual dosage infliximab in a patient with severe ulcerative colitis – case study

Indywidualizacja terapii infliksimabem u pacjenta z ciężkim przebiegiem wrzodziejącego zapalenia jelita grubego – opis przypadku

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infliximab, ulcerative colitis, children

Słowa kluczowe
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Summary

Ulcerative colitis is one of inflammatory bowel diseases. Is characterized by continues inflammatory process, starting from rectum to the various stages of the colon. The disease can have a mild presentation as small amount of blood in the stool, or severe exacerbation when patient has several dozen stools. If stools are bloody, they often lead to anemia requiring blood transfusion. Introduction of biological therapy has improved the pharmacological efficacy and reduced the need of colectomy. Infliximab a chimeric monoclonal antibody biologic drug that works against tumor necrosis factor alpha (TNF-α) that has demonstrated good safety and efficacy in patients with ulcerative colitis. The drug is administered intravenously. In the standard treatment regimen, initially the therapy consists of an induction phase where the drug is administered at a constant dose of 5 mg/kg at intervals of 0, 2, 6 weeks. In the event of a good response, the therapy goes into a maintenance phase where the drug is given at intervals of 8 weeks. The following case report shows the therapeutic problems of a patient with severe form of ulcerative colitis. The boy required individualization of infliximab therapy.

Streszczenie

Wrzodziejące zapalenie jelita grubego należy do chorób z grupy nieswoistych chorób zapalnych jelit. Jest to schorzenie obejmujące jelito grube, charakteryzujące się ciągłym stanem zapalnym rozpoczynającym się w odbytnicy i szerzącym się na różną wysokość jelita. Choroba może mieć różnorodny przebieg, od niewielkiej domieszki krwi w stolcu, po silne zaostrzenia, podczas których pacjent odczuwa konieczność oddawania kilkunastu-kilkudziesięciu stolców na dobę. Domieszka krwi w stolcu może prowadzić do znacznej anemizacji, wymagającej wielokrotnych przetoczeń krwi. Wprowadzenie terapii biologicznej poprawiło skuteczność terapii farmakologicznej, zmniejszając w znacznym stopniu odsetek wykonywanych kolektomii. Infliksimab jest przeciwciałem monoklonalnym skierowanym przeciwko czynnikowi martwicy nowotworów (TNF-α), który wykazał dobrą skuteczność i bezpieczeństwo u pacjentów z wrzodziejącym zapaleniem jelita grubego. Lek jest podawany dożylnie. W standardowym schemacie leczenia początkowo terapia składa się z fazy indukcyjnej, gdzie lek podawany jest w stałej dawce 5 mg/kg mc. w odstępach 0, 2, 6 tygodni. W razie dobrej odpowiedzi, terapia przechodzi w fazę podtrzymującą, podczas której lek podawany jest w odstępach co 8 tygodni. Poniższy opis przypadku ukazuje problemy terapeutyczne pacjenta z ciężką postacią wrzodziejącego zapalenia jelita grubego. Chłopiec wymagał indywidualizacji terapii infliksimabem.

Conflict of interest
Konflikt interesów
None
Brak konfliktu interesów

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CASE STUDY

Almost 17-year-old boy was admitted to hospital in his hometown due to bloody diarrhea. He complained of fatigue. Anemia was observed. Stool culture excluded infectious causes of symptoms. Endoscopy of the lower gastrointestinal tract showed left sided inflammation, highly active, which led to study discontinuation. Sigmoidoscopy gave high suspicion of ulcerative colitis (UC), what was supported by histologic examination. Diagnosis was performed after two weeks from the first symptom. Steroid therapy in dose 40 mg/d was introduced, with good response. However during

prednisone dose reduction to 35 mg/d, the symptoms of bloody stools again occurred. Weight loss was observed. The patient was readmitted to hospital in his hometown, where after exclusion of any gastrointestinal infection, the steroid dose was increased to 60 mg/d. Despite the increasing steroid dose, no significant patient's improvement was observed. After the decision of the parents, the patient was transferred to Our institution. At the time of admission to Our department, the boy complained of fatigue, numerous bloody stools, weight loss of 12 kg was noted. Anemia required blood transfusion. High inflammatory parameters were observed. After obligatory measurement (to exclude any contra-incidence to ciclosporin (CsA) therapy) as magnesium level, kidney assessment with blood pressure evaluation, intra venous CsA was adjusted with conversion to oral intake after good patient reaction. After determination of right dose by proper CsA level in the blood, the patient was discharged to home. Azathioprine (AZA) therapy has been enabled with further steroid dose reduction. Control ambulatory visit showed sustained anemia, but the patient did not complain about any gastrointestinal symptoms, he reported only 2 stools a day. Only lack of weight gain was observed. The dose of ciclosporin was adjusted to the blood level, meanwhile steroids were discontinued. 2 weeks after control visit exacerbation reoccurred. Patient was admitted to Our department. Exclusion of infectious cause was done. The patient had surgical consultation. Patient and parents refused 3 line – surgical therapy and asked for other pharmacological option. After mandatory measurements (RTG, Quantiferon assessment, viral infection exclusion (such as HBV, HCV, HIV)) infliximab (IFX) therapy was introduced. Symptoms of UC were reduced for few days after first IFX dose, nevertheless at other days severe UC signs reappeared. Patient required several blood transfusion. The second IFX dose gave relief of symptoms only for 3 weeks, thus the third IFX dose was adjusted 5 weeks from the first dose. During the third dose of IFX infusion, an allergic reaction was observed. The patient presented face redness with short of breath. The infusion was stopped for 30 minutes, and re-adjusted without any disturbing symptoms. In the following days, improvement of the patient's condition was observed. The patient achieved clinical remission. Due to severe UC type, further IFX therapy was planned at 4-weeks intervals, with additional antihistamine premedication. The boy had infliximab level measurement before adjustment of the fourth IFX dose (4 weeks after 3rd dose). Level was in proper range – 5.2 ug/mL. The patient continued IFX therapy performed with 4-weeks interval between doses until he was 18 years old. No AE was reported, neither during IFX infusion or at time between the doses. During all maintenance IFX therapy the boy presented clinical remission.

DISCUSSION

Case report shows a patient with severe ulcerative colitis. Patients failed first steps of conventional therapy. UC standard therapy includes steroid therapy, and if it not works ciclosporin or infliximab treatment as second-line treatment. Actual consensus for managing acute severe ulcerative colitis in children from 2011 suggest, that after the second line pharmacological treatment failure, surgical option should be introduced (1). Moreover, consensus does not recommend the use of sequential therapy as infliximab shortly after CsA or vice versa. Authors highlight the lack of evidence on the safety and efficacy of this treatment in pediatric field. Experiences among adult patients have promising results, because at published in 2012 meta-analysis, even one dose of infliximab gave remission in 13% of patients, and partial response in 74% of cases. Among patients who received 3 IFX doses, remission achieved 60% of them. Nevertheless in 23% of patients from group consisted of 47 patients, an adverse event (AE) was observed, in which one SAE (severe adverse event) resulted in death (2). Other studies supported conclusion, that sequential therapy can led to avoid colectomy, nevertheless high rates of AE suggest that this type of treatment decision should be performed individually (3, 4). In the presented case, patient and parents did not want to agree for surgical option. Use of infliximab was a rescue therapy, common decision of patient, parents and clinician.

After first infliximab dose patient presented clinical improvement lasting only several days. Probably benefit may give accelerate the second dose. It some centers in case of acute colitis the second dose is given one week after the first. Nevertheless lack is studies with evaluation safety of that decisions. Our patient received IFX shortly after CsA treatment. The shortening interval between first and second IFX dose could increase the risk of eventual adverse events. The second dose of IFX gave great symptom relief, but it persist short time, symptoms have increased again. Adjustment the third IFX dose 5 weeks after the first one gave possibility for disease control. Measurement of infliximab level after 4 weeks from 3rd IFX dose confirmed that plan to give IFX dose every 4 weeks at maintenance phase was good decision. As we see in table 1 after IFX doses patient weight gain, laboratory values normalized and patient achieved remission.

Tab. 1. Patient's presentation before IFX dose

	1st dose	2nd dose	3rd dose	4th dose	5th dose	6th dose
week from first dose	0	2	5	9	13	17
PUCAI	60	40	30	10	10	10
CRP (n < 0.5)	2.49	6.69	4.02	0.17	0.1	0.03
weight (kg)	57	53	50	61	66	69

Biological treatment is effective and safe treatment in ulcerative colitis (5). In 61% of acute colitis, colectomy was needed at times when biological therapy

was not available (6). Introduction of biological treatment highly reduced this risk. The efficacy in use of CsA and IFX among adult patients with ulcerative colitis is similar (7). There is no pediatric trial comparing both molecules. Consensus suggest to use ciclosporin before infliximab in case when azathioprine therapy was not used never before. In that case ciclosporin induces remission which would be kept at AZA therapy as maintenance treatment. Infliximab therapy is great option, because one drug is responsible for induction and maintenance therapy. Limitation of use anti-TNF therapy can be high cost of that treatment. The benefit may be the introduction of biosimilar which reduced the cost of biological therapy. Other benefit is expected from measurement infliximab level, which is an important step for monitoring and optimizing biological therapy. This analysis can prevent the failure of treatment. Nevertheless to date, there is only few studies in pediatrics reporting experience with IFX level monitoring. They are mainly retrospective and most of them assess Crohn's disease patients (8, 9). Studies mainly evaluate the use of this measurement of infliximab level in maintenance therapy to distinguish patients with IFX response loss. Single studies analyzed IFX level among UC patients. Result of Merras-Salmo and Kolho study suggest that patients with UC had higher trough level in comparison with CD patients (10). Other study confirm that greater benefit can be achieved by shortening interval of the IFX dosing than by increasing each dose (11). Assessment of IFX level at Our patient after 4 weeks from 3 IFX dose showed proper drug level. Probably shortening interval between IFX doses prevented therapy failure.

CONCLUSIONS

Individual dosing of infliximab led to remission of disease in our patient. Our experience suggests that patients with acute colitis who have improved after first IFX dose, may have benefit from individualization of infliximab dosage. Future studies may focus if induction regime 0, 2, 6 weeks at severe ulcerative colitis is appropriate, or if should be modified to shorter interval between doses.

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