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Switching Between Infliximab Originator and Biosimilar in Paediatric Patients with Inflammatory Bowel Disease. Preliminary Observations

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Abstract

Background and aims: The growing incidence of inflammatory bowel disease (IBD) in children necessitates the use of biological treatments. Recently, an infliximab biosimilar was authorized in the European Union, which may result in switching patients. We present our preliminary experiences with such switches.
Methods: The prospective study included 32 paediatric patients diagnosed with Crohn's disease (CD) and 7 children with ulcerative colitis (UC) at 3 academic hospitals, who were switched from infliximab originator to its biosimilar (Remsima). Patient characteristics, disease severity, laboratory parameters and adverse events were recorded. Means, medians and ranges were calculated.
Results: Mean age at diagnosis of CD and UC was 11.1 (2.7–15.3) and 12.3 years (8.5–14.8), respectively. Mean number of infliximab originator infusions before switching to the biosimilar was 9.9 (median 8, range 4–29) and 5.1 (5, 1–12) for the CD and UC group, respectively. Evaluation efficacy of last biosimilar doses of all patients revealed rates of clinical remission of 88 and 57% for CD and UC patients, respectively. Last follow-up assessment of patients who continued with biosimilar therapy showed that 16/20 (80%) CD patients and all 4 UC individuals were in remission. One infusion reaction to infliximab biosimilar was observed in a CD patient, which led to treatment discontinuation. The incidence of sporadic mild adverse events prior to and after switching did not differ significantly and was consistent with the safety profile of the infliximab molecule.
Conclusion: Switching from infliximab originator to its biosimilar seems to be a safe option in children with CD. After the switch the biosimilar was just as effective as the originator.

Key Words: Biosimilar; infliximab; inflammatory bowel disease; paediatric

1. Introduction

The number of patients treated with biological agents continues to increase. These medications play an important role in the management of Crohn's disease (CD) and ulcerative colitis (UC).[1] Infliximab was the first anti-tumour necrosis factor α (TNF-α) monoclonal antibody approved for use in inflammatory bowel disease

(IBD). Several randomized and observational studies showed that maintenance therapy with infliximab is effective in a large proportion of paediatric IBD patients.[2–6] Moreover, these studies provided data on the safety profile of infliximab. A biosimilar is a biological medicine that is similar to another biological already been authorized for use. Authorization of a new drug in the European Union requires approval from the European Medicines Agency (EMA). Application for EMA approval should be preceded by clinical studies of the new molecule. CT-P13 (clinical development name for Remicade's biosimilar) was the subject of two randomized trials, both in rheumatoid diseases, aimed at establishing its similarity to the reference product.[7,8] Both studies documented equivalent efficacy, tolerance and safety profiles of the two medicines. On the basis of these findings, the EMA not only authorized two products containing infliximab biosimilar (Remsima, Celltrion Healthcare Hungary Kft and Inflectra, Hospira UK Ltd) for rheumatoid disease, but also extrapolated this approval to all indications for which the reference product is labelled. Based on this evidence-based decision, infliximab biosimilar is labelled for treatment of CD and UC also in the paediatric population.[9]

Clinical development of infliximab biosimilar also included extension trials in which patients who had been treated with the reference product for 1 year were switched to the biosimilar for the second year of treatment. The results of these trials, which included patients with rheumatoid arthritis and ankylosing spondylitis, indicated that switching is safe, does not increase adverse event and immunization rates, and allows the clinical response to be maintained.[10,11] According to a recently published position paper, patients with IBD can be switched from infliximab originator to its biosimilar under the supervision of the treating physician, but only with the patient's consent.[12] The EMA does not regulate interchangeability or automatic pharmacy substitution, leaving this question to the discretion of national authorities.

Due to the legal regulations of 2014, the majority of Polish patients treated with infliximab originator were switched to its biosimilar. This switching resulted partially from the unavailability of the originator, but occurred with the knowledge of both treating physicians and their patients.

To the best of our knowledge, this paper is the first to report experiences with paediatric patients with CD and UC who have been switched from the reference drug to infliximab biosimilar (CT-P13, Remsima).

2. Methods

This prospective study, conducted in three Polish academic centres, included all paediatric patients who had been treated with infliximab preparations and were switched from an infliximab originator to its biosimilar (CT-P13, Remsima) between June and October 2014. In all cases, the reason for switching to the biosimilar was lack of infliximab originator, resulting from administrative restrictions. Informed consent of parents and patients was required prior to switching. Patients were assessed after at least 1 infusion of infliximab biosimilar. Demographic data, disease characteristics, data on infliximab originator and biosimilar infusions, concomitant treatments, clinical outcomes and adverse events were collected. Patients were diagnosed with CD or UC based on clinical presentation, endoscopy with histopathological examination of biopsy specimens and diagnostic imaging. Infliximab originator was started due to the presence of severe luminal CD and/or perianal involvement that proved to be resistant to standard treatment. Patients with UC were qualified to receive infliximab therapy due to exacerbation of the disease and/or resistance to steroids. Activity in CD was assessed on the basis of the Pediatric Crohn's Disease Activity Index (PCDAI). Remission of CD was considered whenever the PCDAI was <10 or <7.5 without the 'height' item. In UC a Pediatric Ulcerative Colitis Activity Index (PUCAI) <10 indicated remission.[13–15] Individuals who were referred to adult gastroenterology centres or discontinued treatment due to remission, administrative/financial restrictions on therapy length or adverse events were excluded from further analysis. All data were expressed as means or medians, standard deviations and ranges. Statistical analysis was conducted with the Wilcoxon signed rank test.

3. Results

3.1. Patient characteristics

A total of 32 paediatric patients with CD and 7 paediatric patients with UC were switched from infliximab originator to CT-P13 biosimilar. Demographic and clinical characteristics of these patients are summarized in Table 1. Mean age at the time of CD and UC diagnosis was 11.1 ± 3.3 and 12.3 ± 2.3 years, respectively. Twenty-six out of 32 (81%) CD patients were anti-TNF-naive. Five patients with CD had previously been treated with infliximab and 1 received adalimumab, with an average number of 11 (range 9–15) infusions/injections per subject. Mean time without biological medication between the previous and actual course of therapy was 11 months (SD = 7.5, range 5–25). One patient with UC had an 11-month history of infliximab therapy continued up to 1 year prior to the current treatment. All subjects stopped previous biological treatment due to remission/administrative restrictions. Mean PCDAI at qualification of CD patients for actual treatment with infliximab originator was 49 ± 12 (range 15–65). In 25/32 (78%) patients PCDAI exceeded 51, and 7/32 (22%) individuals had perianal disease. Mean PUCAI at qualification of UC patients for actual treatment with infliximab originator was 43 ± 18 (median 45, range 10–65).

3.2. Efficiency of switching CD patients from infliximab originator to its biosimilar

Mean time elapsed between the beginning of infliximab therapy and switching to the biosimilar was 67 weeks (median 46 weeks, range 22–224 weeks). Mean number of infliximab originator infusions given prior to switching was 9.9 (range 4–29) per patient. All patients completed induction therapy with infliximab originator. Seven patients were switched to biosimilar shortly after induction, and their first dose of biosimilar corresponded to the 5th dose of infliximab overall. The assessment after the last dose of Remicade, shortly before switching, showed that 26/32 (81%) patients received infliximab originator (5 mg/kg) at 8-week intervals. In another 6 patients the intervals between consecutive doses of infliximab originator were shorter; 4 out of these 6 patients had PCDAI >51 at qualification. In 5 patients the decision to shorten the interval between consecutive doses to 4 weeks was made after the 4th, 6th, 7th, 8th and 24th administrations of Remicade, respectively. In another patient, the interval was shortened to 6 weeks beginning with the 9th dose of infliximab originator. The reason for altering the administration frequency in this patient was the loss of therapeutic response before the end of the 8-week interval.

Examination after the last dose of Remicade, shortly before the first infusion of infliximab biosimilar, showed that 22/32 (69%) patients presented with clinical remission. Another 10/32 (31%) patients presented with the active (mild/moderate) form of the

Table 1. Characteristics of the study participants.

Characteristic	Crohn's disease (n = 32)	Ulcerative colitis (n = 7)
Age at diagnosis (y)	11.1 ± 3.3 (2.7–15.3)	12.3 ± 2.3 (8.4–14.8)
Paris classification of Crohn's disease (n)		
A1a/A1b	8/24	NA
L1/L2/L3/L4a/L4b*	8/9/12/5/2	NA
B1/B2/B3/B2B3/p	20/8/0/4/7	NA
Paris classification of ulcerative colitis (n)		
E1/E2/E3/E4**	NA	1/1/0/5
S0/S1	NA	1/6
C-reactive protein at qualification (mg/dl)	1.6 ± 1.9	0.3 ± 0.3
Erythrocyte sedimentation rate at qualification (mm/h)	28 ± 21	32 ± 29
Haemoglobin at qualification (mg/dl)	12.2 ± 1.4	10.1 ± 1.9
Mean PCDAI/PUCAI at biological therapy onset	49 ± 12 (15–65)	43 ± 18 (10–65)
Time from diagnosis to start of current infliximab originator (year)	1.8 ± 1.2 (1 wk to 5 y)	1.7 ± 1.7 (0.5–4.8)
No. of infliximab originator administrations	9.9 ± 6.4 (4–29)	5.1 ± 3.8 (1–12)
Concomitant medication	5-ASA, 1; AZA, 8; AZA and 5-ASA, 11; MTX, 1; MTX and 5-ASA, 8; no other treatment, 3	5-ASA, 3; AZA, 1; AZA and 5-ASA, 3

Data are presented as mean ± SD and range when appropriate.

5-ASA, 5-aminosalicylic acid; AZA, azathioprine; MTX, methotrexate; PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Activity Index.

*Patient could have more than one location; **1 patient with unknown disease extent.

disease. The latter group included 3 patients who were switched to biosimilar shortly after induction, and their first dose of biosimilar corresponded to the 5th dose of infliximab overall. All 32 patients received at least 2 doses of Remsima. After treatment with the biosimilar, clinical remission was documented in all 3 patients who were switched to Remsima shortly after induction and presented with active disease at the time of switching. This was reflected by a higher overall remission rate. The results of treatment with infliximab originator and up to 2 infusions of the biosimilar are summarized in Table 2. Mean values of PCDAI prior to and after switching are presented in Figure 1. The switching-related change in PCDAI was statistically significant ($p < 0.05$).

The last assessment took place 11 months after the first patient had been switched, after a mean follow-up of 8 ± 2.6 months (range 2–11 months). The mean number of biosimilar infusions given up to the end of the follow-up period was 5.7 (median 5, range 2–13). Due to different times of switching and discontinuation of treatment in some cases, our patients differed considerably in terms of the number of biosimilar infusions received: 3 (n = 30), 4 (n = 29), 5 (n = 20), 6 (n = 14), 7 (n = 9), 8 (n = 5) or 9 (n = 4) doses of infliximab biosimilar were administered. Furthermore, our series included 2 patients who were given up to 13 infusions of biosimilar at 4-week intervals.

The group of patients in remission at the time of switching (22/32, 69%) maintained remission after the 2nd dose of biosimilar. One patient, who remained in remission throughout the follow-up period, reported abdominal ache and depression of mood during the last assessment (after the 4th biosimilar dose), and was eventually classified as presenting with a mildly active form of the disease. Among 10 patients presenting with active disease at the time of switching, 7 achieved clinical remission during further follow-up. Overall, 88% (28/32) patients were in clinical remission at the end of the follow-up period.

During biosimilar therapy, another 2 patients required the interval between consecutive doses to be shortened to 4–6 weeks after the 2nd administration of Remsima due to the presence of mild disease symptoms (abdominal ache, loose stools).

At the time of writing, 20 patients were still on biosimilar therapy; 16 of them (80%) were in clinical remission during their last assessment. The subset of 4 patients without remission included 3 individuals who were not also in remission at the time of switching.

To summarize, at the end of the follow-up period 20/32 patients (63%) were still on maintenance remission therapy: 15/20 received infliximab biosimilar every 8 weeks and another 5 at shorter intervals. Twelve of the 32 children stopped the treatment: 3 patients in remission were referred to an adult centre, 2 lost therapeutic response, 1 had an allergic reaction during infliximab infusion, 1 was switched to adalimumab due to dermatitis, and 5 finished therapy in remission due to financial constraints.

3.3. Efficiency of switching UC patients from infliximab originator to its biosimilar

The assessment conducted shortly before switching showed that all patients received infliximab originator (5 mg/kg) at 8-week intervals. Mean number of infliximab originator infusions given prior to switching was 5.1 (range 1–12) per patient. Two patients were switched during induction therapy, after the 1st and 2nd dose of originator, respectively. Another patient was switched shortly after induction, prior to administration of the 4th dose. Mean PUCAI at the time of switching was 16.4 (median 20, range 0–30); 2/7 (29%) patients were in remission. Mean duration of follow-up after switching was 5 ± 3.6 months (range 0–9 months). Mean PUCAI values determined prior to the 2nd and 4th doses of Remsima were 11 (median 0, range 0–40) and 2 (median 0, range 0–5), respectively.

Only 4 out of the 7 patients (57%) were continuing biosimilar treatment at the time of writing. All patients presented with clinical remission at the end of the follow-up period. In the case of 1 patient, switched to biosimilar from the 2nd dose of the induction treatment, loose stools with blood were recorded after the 4th dose of infliximab. The interval between consecutive doses was shortened to 4 weeks in this patient, which eventually resulted in remission. Treatment was discontinued in 3/7 (43%) patients. In 1 patient, treatment was discontinued due to an allergic reaction and the patient's mother's decision to change to a different medical centre. Another 1 developed varicella zoster infection after the 1st dose of biosimilar. The 3rd patient required shortening of the interval

Table 2. Outcomes of treatment with infliximab originator prior to and after switching.

	At infliximab originator start	At 2nd to last infusion of infliximab originator	At last infusion of infliximab originator	At switching (shortly before 1st infusion of infliximab biosimilar)	After 1st infusion of infliximab biosimilar	After 2nd infusion of infliximab biosimilar	Last- follow up assessment
Week	–	−16	−8	0	+8	+16	Different for each patient
No. of patients evaluated	32	32	32	32	32	30	20
Remission rate	–	–	–	69%	75%	83.3%	80%
PCDAI	49 ± 12	7 ± 10	6.6 ± 8.6	8.8 ± 9.8	7.2 ± 8.8	5.6 ± 7.8	6.6 ± 10.6 (2.5; 0–42.5)
	(15–65)	(3.75; 0–32.5)	(5; 0–30)	(5; 0–35)	(5; 0–30)	(3.8; 0–30)	
CRP (mg/dl)	1.6 ± 1.9	0.5 ± 0.7	0.55 ± 0.77	0.58 ± 0.85	0.55 ± 0.63	0.52 ± 0.7	0.57 ± 0.75 (0.11; 0–2.8)
	(1.05; 0–7.8)	(0.3; 0–2.3)	(0.4; 0.01–3.81)	(0.25; 0.01–3.8)	(0.3; 0.01–2.1)	(0.3; 0.01–2.7)	
ESR (mm/h)	28 ± 21	13 ± 13.5	15 ± 14	14 ± 13.8	14 ± 17	14 ± 16	18 ± 14.6 (12.5; 1–58)
	(23; 3–80)	(9; 0–63)	(10; 2–59)	(9; 1–63)	(8; 0–75)	(9; 1–80)	
Platelets	393 ± 108	302 ± 81	299 ± 82	304 ± 112	326 ± 117	306 ± 107	326 ± 108 (305; 181–587)
	(392; 169–630)	(305;112–543)	(287; 171–635)	(282; 183–804)	(315; 175–854)	(290; 186–809)	

Mean ± SD and range are given where appropriate.
Median ± SD and range are given where appropriate.
CRP, C-reactive protein; ESR erythrocyte sedimentation rate; PCDAI, Pediatric Crohn's Disease Activity Index.

between consecutive doses to 4 weeks, and eventually was switched to adalimumab after the 7th dose of Remsima due to loss of therapeutic response.

3.4. Safety

One adverse event was recorded during infusion of infliximab biosimilar to a CD patient. The patient showed an allergic reaction during administration of the 4th dose after switching, which eventually resulted in discontinuation of the treatment. In the case of this patient, the actual course was the 1st course of infliximab therapy.

All patients were asked to report any infection or other health problems emerging between administration of consecutive doses of infliximab biosimilar. Typically, mostly mild infections of the upper respiratory tract were reported (7/32, 22%). Data on adverse events are summarized in Table 3.

In 12 out of the 32 (38%) children, episodic mild symptoms of CD (abdominal ache, aphthous stomatitis, loose stools) were observed during the follow-up period. Three patients required surgery due to CD-related complications (stenosis, abscess). All surgical interventions were conducted during the course of biosimilar therapy. All 3 surgically treated patients belonged to the group with mild/moderate disease, with PCDAI ≥25 at the last assessment before switching.

Due to the presence of mild disease symptoms, 2/7 UC patients required shortening of the interval between consecutive infliximab doses to 4 weeks. In the case of 1 patient, biological treatment was stopped after the 1st dose of infliximab biosimilar due to the development of varicella zoster infection.

4. Discussion

Our study has provided the first evidence of infliximab biosimilar efficiency in children with IBD who required switching from infliximab originator to its biosimilar during the course of biological therapy. All CD patients were switched during remission maintenance therapy after induction therapy with infliximab originator. After the last dose of Remicade, 22/32 (69%) patients were in remission, 9/32 (28%) presented with mild disease activity and 1/32 (3%) with moderately severe CD.

Eight out of the 32 CD patients (25%) required shortening of the interval between consecutive infliximab doses. In 7 patients, more frequent infusions were required after approximately 1 year of the therapy, and 1 individual showed initial evidence of therapeutic response loss after the 25th dose. In 6/8 patients, the decision to shorten the dosing interval was made during therapy with infliximab originator, and in another 2 patients after 1 dose of biosimilar. De Bie et al.[16] reported that 13% of patients required repeated infusions after 1 year and 40% after 3 years of treatment. The differences from our findings might be related to the fact that our patients presented with a more severe form of CD at the onset of biological treatment, as well as to other characteristics of the study participants. At the end of the follow-up period, nearly 1 year after the first patient had been switched to infliximab biosimilar, there is no evidence suggesting that switching may shorten the interval between consecutive infliximab doses.

No spontaneous exacerbation of the disease was observed after switching, and an improvement was documented even in 7 patients who presented with mild/moderate disease prior to administration of infliximab biosimilar. Three of 10 patients presenting with mild disease received 4 doses of infliximab originator; after switching they all achieved remission after the 2nd dose of infliximab biosimilar.

However, it is difficult to assess whether this was a consequence of better therapeutic response to infliximab biosimilar or of a longer treatment time.

Only 4/7 patients with UC remained on maintenance therapy at the end of the follow-up period. All of them continued therapy while in clinical remission. This group was more heterogeneous than individuals with CD, as some UC patients had already been switched to infliximab biosimilar during the course of induction therapy. This fact seriously limits the possibility of comparing Remicade and infliximab biosimilar in terms of efficiency.

Data on the use of infliximab biosimilar in patients with CD and UC are scarce. To the best of our knowledge, there is only 1 published study in which IBD patients were switched to infliximab biosimilar. Jung et al.[17] described a group of 27 adults with CD who were switched to infliximab biosimilar. Up to 92.6% of these patients remained in remission, which was similar to the proportion before switching. The same authors followed 9 patients with UC; 66.7% of them showed a good response after switching to infliximab biosimilar. All our 32 patients were assessed after the last dose of biosimilar; remission was documented in 88 and 57% of individuals with CD and UC, respectively. On further follow-up, all patients with UC and approximately 80% of subjects with CD patients, who continued therapy with infliximab biosimilar, presented with remission. Nevertheless, our findings are highly consistent with the data published by Jung et al.[17]

Therapy was discontinued due to an adverse event observed during infusion of infliximab biosimilar in only 1 of our CD and UC patients. Twenty-two percent of CD patients suffered from mild upper respiratory tract infections, which is consistent with the results of previous studies, in which similar infections were recorded in 15–37% of participants.[4,5] No serious opportunistic infections were recorded in our series. Three of 32 patients with CD required surgery during the course of biosimilar therapy due to complications of the primary disease. This likely reflected the high degree of severity of CD at the onset of biological therapy; all these patients presented with PCDAI ≥25 at the time of switching. Jung et al.[17] did not observe any adverse events in their UC group, but, as in our study, 1 patient with CD required discontinuation of treatment due to adverse events. Lack of other complaints in Jung et al.'s series might reflect different characteristics of their patients.

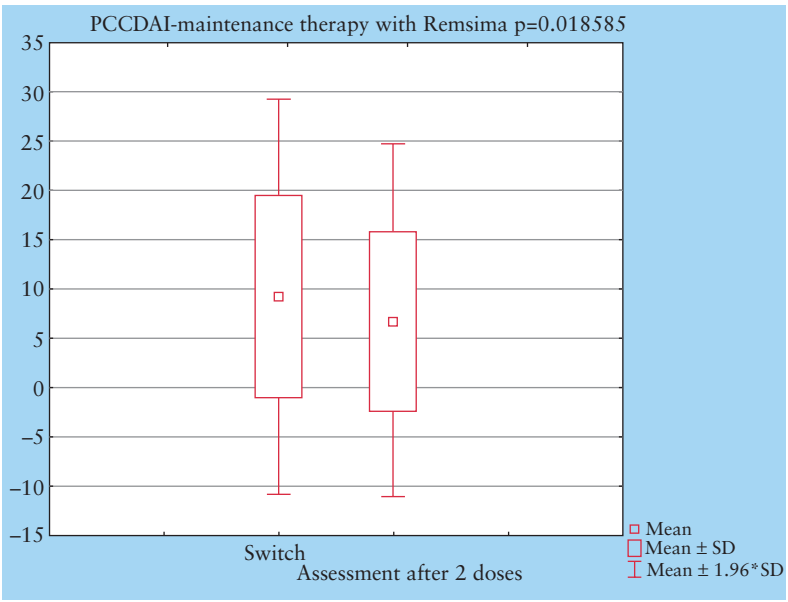

Figure 1. Maintenance of remission with Remsima.

Table 3. Adverse events recorded during biosimilar therapy.

Adverse events during therapy with infliximab biosimilar	No. of patients with Crohn's disease	No. of patients with ulcerative colitis
Infusion reaction (resolved after histamine receptor H1 antagonist administration)	0	2 (after switching)
Infusion reaction (treatment termination)	1 (after switching)	0
Infections of upper respiratory tract	7	0
Viral diarrhoea	2	0
Nausea, headache	2	0
Seborrhoea	1	0
Epistaxis	1	0
Conjunctivitis	1	0
Pneumonia	1	0
Stenosis, abscess	3	0
Ovarian teratoma (complete surgical resection of the ovary; surgery was performed between consecutive infliximab doses; no dose modification was necessary)	1	0
Varicella zoster (treatment termination)	0	1

The most important limitation of our study stems from heterogeneity in the time of switching to infliximab biosimilar during the course of therapy. Some patients were switched shortly after induction therapy (CD group) or even during the induction phase (UC group). Another limitation may be related to different times of treatment termination after switching. Typically, treatment was stopped due to transfer of patients to an adult gastroenterology centre or because of financial/administrative constraints. As a result, we were not able to assess the long-term effectiveness of biosimilar therapy in all patients. Furthermore, the children included in our series were highly heterogeneous in terms of age and disease localization, and only some of them were anti-TNF-naive.

4.1. Conclusion

This analysis showed that treatment with infliximab originator and biosimilar produces similar results. Infliximab biosimilar seems to be as effective and safe as its originator. However, head-to head comparison is needed to confirm our findings.

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Conflict of Interest

J. Kierkus reports having received speaker fees from Egis, MSD and AbbVie.

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Author Contributions

Joanna Sieczkowska: conception and design of the work, data acquisition/analysis/interpretation and drafting/final approval of the article. Dorota Jarzębicka: conception/design of the work, data acquisition/analysis/interpretation and drafting/final approval of the article. Aleksandra Banaszkiewicz: data acquisition/analysis/interpretation and drafting/final approval of the article. Anna Plocek: data acquisition/analysis/interpretation and drafting/final approval of the article. Agnieszka Gawronska: data acquisition/analysis/interpretation and drafting/final approval of the article. Ewa Toporowska-Kowalska: data acquisition/analysis/interpretation and drafting/final approval of the article. Grzegorz Oracz: data acquisition/analysis/interpretation and drafting/final approval of the article. Monika Meglicka: analysis of data and final approval of the article. Jaroslaw Kierkus: conception and design of the work and final approval of the version to be published.

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