Analyses of health related quality of life, bone methabolism and vitamin D level in children with Crohn disease treated with infliximab

Doctoral theses

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Introduction

Inflammatory bowel disease (IBD) significantly encumbers patients life, and its treatment is a challenge for doctors as well. Pathogenesis of these diseases has not been fully explained yet, however, final healing of Crohn's disease (CD) and ulcerative colitis is not conceivable without clarification of reasons. Knowhow related to aforementioned disorders continuously broadens, more and more risk factors have become transpired. Based on our current knowledge, collective of genetic susceptible, circumferential factors and abnormal immune response are needful for formation of disorders. In the recent few years a new feasible therapy for children with IBD has appeared: anti-tumor-necrosis-α (anti-TNF-α), namely infliximab (IFX) and adalimumab (ADA). Usage of IFX in early life has been reported in several international studies, however, inland experience is limited up to now.

Chronic CD through severe state often issues in quality of life decrease in children. Reasonably, such disorders and related problems (e.g.: loss of performance in school, integration to communities) are huge charge on young patients. As medical doctors we reckon assessment and improvement of quality of life as utmost importance, and not seeking after normalization of laboratory parameters only. Therefore, an emphasized part of our study has been the follow-up of quality of life in severe, therapy resistant children with CD, treated with infliximab (available in Hungary since 2009). Furthermore, disease activity and clinical parameters have been monitored as well.

CD doesn't respect intestinal track only, but affects bow metabolism and mineral density, which undisturbed development in childhood is very important. Disturbances in skeletal system may have severe impact on the whole life. In addition, many studies report about significant effect of vitamin D on physical functions, acting the key part of bone metabolism. Consequently, in the second part of our study we have aimed to measure and assess the bone metabolism and vitamin D level of children with severe CD, treated with infliximab.

We expect that our results contribute to deeper knowledge of quality of life and bone metabolism of children with CD.

Aims

In the scope of our study we have assessed the effect of IFX therapy on quality of life, disease activity (PCDAI), and laboratory parameters of children with CD at 1st Department of Pediatrics, Semmelweis University. Furthermore, we have examined the changes in bone metabolism and vitamin D level during the one year IFX treatment period. Main questions and aims have been the followings:

1 Changes in quality of life and laboratory parameters of conventional therapy resistant children with severe CD during one year IFX therapy.

1. How does the quality of life (IMPACT-III) of children change during the one year IFX therapy?
2. Can regression (auto-, cross regression) be confirmed between quality of life and certain clinical and laboratory parameters?
3. What is the reliability of IMPACT-III questionnaire, used in Hungary for the first time, like?
4. How does the diseases activity index (PCDAI) develop during the one year IFX therapy?
5. How do the CRP, albumin and platelets develop during the one year IFX therapy?

2 Changes in bone metabolism and vitamin D level during the one year IFX therapy.

1. How do bone metabolism serum markers develop during the one year IFX therapy?
2. What is bone mineral density of our patients like? Does is change during the one year IFX therapy?
3. What is serum vitamin D level of our patients like? How does it change due to one year IFX therapy?

4. Can seasonal variability in serum vitamin D be discovered in children with CD?
5. Does seasonal variability change due to one year IFX therapy?

Patients and method

1 Follow-up of quality of life, disease activity, and laboratory parameters

1.1 Patients

In our prospective study, performed at the 1st Department of Pediatrics, Semmelweis University in Budapest, Hungary, 51 children with severe CD resistant for conventional therapy (azathioprine, steroid) were involved. Of the 51 children 30 (58.8%) were girls, the mean age was 15.25 year (ranged: 11-18 years). The results of IMPACT-III, the analysis of clinical indicators, like PCDAI and laboratory parameters were registered at every visit in 40 cases. Regression analysis of quality of life was based on the data of all 51 children.

1.2 Therapy procedure, methods, and statistical analyses

According to international recommendations, IFX at a dose of 5 mg/kg intravenous infusion was applied as induction therapy at week 0, 2 and 6, and as maintenance therapy at every following 8 week. The investigated parameters were registered at week 0, 6, 30 and 53.

1.2.1 *IMPACT-III*

To measure health-related quality of life for the first time in Hungary (validated in 2008), the IMPACT-III questionnaire was applied. This specific self-report questionnaire was developed for youth with IBD at the age between 9 and 17 years. It consists of 35 queries covering 6 domains: bowel symptoms, systemic symptoms, emotional functioning, social functioning, body image and treatment/interventions which allow us to analyse each domain

separately. Children indicated the extent on a 5 point Likert scale to which they are belonging by specific aspects of their health condition. Possible scores range from 35 to 175, the higher score indicates better quality of life.

1.2.2 *PCDAI*

PCDAI measures patient's status according to a score-system with a maximum of 100 points. It is based on anamnestic data (abdominal pain, stool quality and number, general well-being), laboratory parameters (hematocrit, CRP, serum albumin), and physical status (body weight change, rate of body height growth, abdominal sensitivity, perianal disease, extraintestinal manifestation). Disease with PCDAI score higher than 30 is considered as to be severe.

1.2.3 *Statistical analyses*

Due to non-normal data distribution, Friedman test and Wilcoxon single rank test with Bonferroni analysis as post-hoc test were applied to follow up the changes of each variable through the treatment period (IBM® SPSS® 20, Chicago, IL). P values lower than 0.05 were accepted as statistically significant. Correlation between IMPACT III and PCDAI was assessed by Spearman's rank-order correlations (IBM® SPSS® 20, Chicago, IL).

To test the reliability of IMPACT-III Cronbach's alpha was determined (IBM® SPSS® 20, Chicago, IL).

1.2.4 *Autoregressive cross-lagged analyses*

To examine the relationships between QoL (IMPACT-III) and clinical- and laboratory parameters an autoregressive cross-lagged model (ARCL) was applied (Mplus 6.01). If the value at the time of T can be predicted by the value at the time of the previous time, T-1, then autoregression stands. Moreover, if two or more parameters interaction is of interest, then cross-lagged pathways can be analysed. To evaluate the overall model fit, absolute fit index (chi-square value), comparative fit index (CFI), Tucker-Lewis Fit Index or non-normed

fit index (TLI or NNFI), and root mean square error approximation (RMSEA) were calculated.

2 Follow-up of changes in bone metabolism and serum vitamin D level

2.1 Patients

Our prospective study was also performed in the 1st Department of Paediatrics of Semmelweis University. Fifty children with moderate to severe CD, resistant to conventional therapy (azathioprine, systemic steroid) were involved in the analysis of the vitamin-D level, bone markers and mineral density changing during the one year IFX therapy. The mean age was 14.8 year (ranged: 8-18.6 years), and of these 50 children 31 (62%) were girls. The mean time since diagnosis was made 2.1 years (range: 0.1–7.9 years).

2.1.1 *Seasonal variability of serum vitamin D level*

For monitoring the seasonal variability of serum vitamin-D level additional 25 children with CD treated with IFX were involved. So, 39/75 (mean age of 14.6 year) and 36/75 (mean age of 14.7 year) patient's data was post processed in the summer and winter period, respectively.

2.1.2 *Control group*

Control group were formed from 34 children with CD in clinical and IFX free remission. The mean age was 14.5 year, and of these 34 children 19 (55.8%) were boys. The mean time since diagnosis was made 3.15 years. IFX therapy in the control group was considered as exclusion factor.

2.2 Therapy procedures, methods, and statistical analyses

IFX therapies were conducted according to international and national recommendations, as it has been already presented above.

For at least 3 months before the IFX therapy started and during the therapy vitamin-D and calcium were supplemented in a dose of 1000

U/day and 500 mg/day in all patients (patients treated with IFX, as well as control group), respectively.

The investigated parameters were registered at week 0, 6, 30 and 53.

2.2.1 *Bone markers*

As markers of bone metabolism and bone turnover, levels of serum OC and β-isomerized C-terminal telopeptide fragments of collagen type I (beta-CrossLaps, bCL) were measured at dates described above. Immunoassay analyses were carried out with electrochemiluminescence immunoassay (ECLIA) methods (Elecsys N-MID Osteocalcin and Elecsys beta-CrossLaps, Roche®) at Central Labor of Semmelweis University.

2.2.2 *Serum vitamin D*

Immunoassay analyses for determination of 25(OH) vitamin D were carried out with chemiluminescence immunoassay (25-OH Vitamin-D, LIAISON®, DiaSorin). Based on the recent guideline of the Endocrine Society published in 2011, level of ≤20 ng/mL as vitamin-D deficiency and of 21–29 ng/mL as insufficiency was defined.

Based on the date of the first IFX therapy seasonal variability of vitamin-D level was measured. Summer period was defined from 21th of March till 22th of September and the rest of the year defined as winter period.

2.2.3 *Bone mineral density*

Whole-body and lumbar spine Dual-energy X-ray absorptiometry (DEXA) scans, performed at 2nd Department of Pediatrics of Semmelweis University, were used primarily to evaluate bone mineral density status. All scans were performed by the same operator and with the same machine (type: QDR Discovery, model: Discovery A (S/N 83638), manufactured by HOLOGIC, Inc., USA). The scan provided measurements of lumbal and whole-body areal

BMD (g/cm2). According to literature, Z-score less than -2.0 was considered as reduced bone mineral mass.

2.2.4 *Statistical analyses*

All analyses were conducted by using SPSS® 22 (IBM®, Somers, NY). Friedman test as non-parametric test and paired t-test as parametric probe were run to determine significance levels. Statistical significance was accepted at $p<0.05$ level with 95% confidential interval. As post-hoc test Bonferroni analyses were applied. To determine the correlation between the laboratory and clinical parameters Spearman correlation coefficient were calculated.

Results

1 Follow-up of quality of life, PCDAI, and laboratory parameters

1.1 Development of quality of life and clinical parameters during the one year IFX treatment

1.1.1 *IMPACT-III*

The IMPACT-III score used to measure quality of life of patients with CD improved significantly due to one year IFX treatment ($\chi^2_{=}58.101$; $p<0.001$). The IMPACT-III median score at week 0 was 115, which improved to 142 by week 6. Long term results also support significantly better quality of life compared to initial status.

The IMPACT-III questionnaire allows us to evaluate the 6 domains separately. Each domain noticed significantly ($p<0.01$) better median score during the examined period than at the time of initial. The systemic symptoms domain improved the most.

1.1.2 *Autoregressive cross-lagged analysis*

To analyse the relation between quality of life and other clinical parameters four ARCL models were studied:

Model 1: ARCL model of IMPACT-III and PCDAI
Model 2: ARCL model of IMPACT-III and CRP levels
Model 3: ARCL model of IMPACT-III and serum albumin levels
Model 4: ARCL model of IMPACT-III and platelets levels

Result of the nesting analysis showed that Model 1 was a well-specified model, fitted the data the best: $\chi 2=11.53$, CFI=1.0, RMSEA= 0.0. CFI and RMSEA of the other 3 models indicated poor fit.

Excluding the regression of PCDAI between week 0 and week 6 in Model 1, all autoregressive pathways between the regular visits were significant within each model. Moreover, the highest relation was observed between week 30 and week 53 in every grade.

Cross-lagged association was observed in Models 2, 3, and 4; however, it should be kept in mind that these models did not fit well.

1.1.3 *Reliability analysis of IMPACT-III questionnaire*

To assess reliability of IMPACT-III questionnaire, Cronbach's alpha value was determined, which indicates an excellent level of internal consistency for our IMPACT-III scale with this specific sample. Corrected item total correlation was checked, 3 out of the 35 questions showed weaker index, however, Cronbach's alpha did not change considerably, the advance is not remarkable.

1.1.4 *Development of PCDAI during IFX treatment*

Both short and long term results showed significant decrease in PCDAI ($\chi 2=59.492$, $p<0.001$) during the period of one year infliximab treatment compared to the initial scores.

Based on PCDAI scores, more than half of the patients were in remission at every monitoring time: 58.8%, 65.1% and 61.9% at week 6, week 30 and week 53, respectively.

1.1.5 *Development of laboratory parameters during the one year IFX therapy*

CRP, platelets level and albumin level decresed significantly ($p<0.001$) during the therapy course.

1.2 Development of bone metabolism and serum vitamin D level during the one year IFX therapy

1.2.1 *Development of bone markers*

Serum OC levels increased significantly under IFX therapy ($\chi 2=18.61$, $p<0.001$). However, post hoc analysis revealed no significant differences from week 0 to week 53 (median=37.67). Contrarily, there were no significant changes in the levels of serum bCL ($p=0.105$) during one year of IFX treatment.

1.2.2 *Effects of IFX on bone mineral density*

18.3% of the 50 children with CD had reduced lumbal BMD Z-score (BMD Z score < 2.0) prior the IFX therapy. Repeated DEXA result was available in 29 cases. Based on the follow-up analysis there were no significant changes in BMD Z-scores in this regards (lumbal and total body BMD Z-scores were $p=0.985$, and $p=0.155$, respectively).

1.2.3 *Development of serum vitamin D levels in children with CD during the IFX therapy*

There were no significant changes in vitamin D level compared to the initial serum level (median=18.3 ng/ml) by the end of one year period of IFX treatment (median=21.95 ng/ml, $p=0.099$), but short term results confirmed significant improvement by week 6 ($p=0.015$).

Ratio of vitamin-D deficiency and insufficiency were improved by the effect of IFX therapy. The proportion of vitamin-D deficiency decreased to 40.0% from the initial 57.4%. At the initials, 18% of the patient had serum vitamin-D level >29 ng/mL, which increased to 22% by week 53.

Regarding control patients, 25% of them had vitamin-D deficiency and 21% had vitamin-D level higher than 29 ng/mL.

Comparing vitamin-D levels of patients in the control group and of patients treated with IFX, no significant differences were observed. Vitamin-D level of patients in the control group didn't differ

significantly from that of patients before IFX treatment (p=0.093), moreover, no significant differences developed between the two groups by the end of the 1 year IFX treatment concerning those who were in remission (p=0.42).

1.2.4 *Seasonal variability of serum vitamin D*

Seasonal variability was also assessed to determine whether the winter or summer period may influence the vitamin-D status. Indeed, significant difference in the serum level of vitamin-D was observed between summer and winter period at week 0 (p=0.039). However, this significance was not detected after one year IFX therapy (p=0.426). At initials 69% and 19% of patients had severe vitamin-D deficiency, respectively insufficiency in the winter period group, meanwhile, the same values are 48.6% and 28.6% in the summer period group.

Improvement of the ratio of vitamin-D deficiency and insufficiency was observed in both groups after one year IFX therapy course.

Conclusions

Based on our study the following conclusions can be derived:

1. In our study we have confirmed improved health related quality of life of conventional therapy resistant children with CD. To measure the quality of life the IMPACT-III questionnaire has been used for the first time in Hungary, which reliability in line with international experiences is outstanding.

2. In the autoregressive cross-lagged analysis (ARCL) of IMPACT-III, PCDAI score and other clinical parameters (CRP, serum albumin, serum platelet number) autoregressive pathways were found within each model. The strongest relation was observed between week 30 and week 53 in every grade. Cross-lagged association was observed in Models 2, 3 and 4 of ARCL, however, due to poor model fit it must be accepted reservedly. We are unaware of ARCL analyses of patients with CD or biological therapy.

3. On the grounds of PCDAI score significant improvement in patient's condition was confirmed during the one year IFX therapy applied according to protocols. Based on PCDAI scores, more than half of the patients were in remission (PCDAI≤12.5) at every monitoring time, which is in line with international experiences.

4. In almost one fifth of our patients reduced bone mineral density was confirmed at the initial of IFX therapy. Based on the follow-up analysis there were no significant changes in it by the end of the one year IFX therapy.

5. Serum OC level as a marker of bone formation increased significantly under the one year IFX therapy. However, post hoc analysis revealed no significant differences between data from initials and from week 53. Contrarily, no significant changes

were confirmed in the levels of serum bCL – marker of bone resorption – during one year of IFX treatment.

6. In more than half of our patients serum vitamin D deficiency was confirmed, which did not improve significantly by the end of the IFX therapy.

7. Significant difference in the serum level of vitamin D was confirmed between summer and winter period at the initials, however, this effect known from literature as well disappeared during the IFX treatment.

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