Management of Infliximab Treated Patients with Psoriasis Based On Infliximab Plasma Levels and Antibodies to Infliximab

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Abstract

Background: Infliximab is the fastest acting biological agent in psoriasis treatment due to the possibility of intravenous administration and a well-conducted induction phase of treatment (week 0, 2, and 6). Another advantage is the weight-based dosing. However, disadvantages include the risk of infusion reactions and the production of neutralizing antibodies that are responsible for the secondary loss of efficacy.

Objectives: To analyze the dynamics of infliximab levels during one maintenance interval as well as the levels of anti-infliximab antibodies in patients with psoriasis treated with infliximab for a period of at least 22 weeks.

Methods: We followed 25 patients with psoriasis treated with infliximab for a period of at least 22 weeks at a dose of 5 mg/kg. Based on the clinical picture at the time of blood sample collection, the patients were divided into responders, partial responders and non-responders. Plasma levels of infliximab and antibodies to infliximab were examined in venous blood samples taken during one maintenance interval. The levels of infliximab were examined in week 0, 2, 4, 6, 7 and 8, anti-infliximab antibodies were examined in week 8.

Results: According to the obtained data of infliximab levels and anti-infliximab antibodies, we divided the patients into 4 groups—responders, responders with shortened period of efficacy, non-responders with production of antibodies, and non-responders without production of antibodies. The dynamics of infliximab levels and the production of anti-infliximab antibodies were characteristic for each group. A definitive therapeutic management was created specifically for each group of patients.

Conclusions: Monitoring the dynamics of infliximab levels and anti-infliximab antibodies is not only of scientific importance, but it may be crucial in daily clinical practice, enabling an objective management of infliximab treatment.

Keywords: Infliximab; Psoriasis; Trough level of infliximab; Antibodies to infliximab; Ati; Treatment

Introduction

Psoriasis is a chronic immune-mediated disease affecting the skin, nails and joints. In recent years it can be effectively treated with biological therapy. In Slovakia, 4 biologicals are approved for the treatment of psoriasis: infliximab, adalimumab, etanercept, and ustekinumab.

To date, biological treatment of psoriasis has been guided solely by the clinical picture and the presence of side effects. Part of clinical trials include drug related pharmacokinetics and immunogenicity. During the clinical trials the formation of antibodies to biologicals was detected. However, antibodies or drug levels are not examined in common practice.

Infliximab has a very good reputation among biologicals used in the treatment of psoriasis. Its advantages are weight-based dosing, very well designed induction phase of treatment (week 0, 2, 6) and intravenous administration. Due to these advantages, infliximab achieves a very rapid onset of action and a good therapeutic effect. Other advantages include a possibility of increase in the dose up to double amount (10 mg/kg) and a possibility of reducing the maintenance interval from initial 8 weeks to 6, or even down to 4 weeks. The disadvantages include infusion reactions, the need for trained medical personnel, adequate equipment of medical facilities, and the formation of neutralizing antibodies, which may be responsible for the loss of response or infusion reactions.

In recent years, immunogenicity of biological substances has been the hottest topic related to biological treatment. Nevertheless, it still does not have application in clinical practice. Since August 2012, we have been monitoring the levels of infliximab (IFX) and anti-infliximab antibodies (ATI) in all our patients with chronic plaque psoriasis treated with infliximab. Based on the obtained results, we divided the patients into 4 groups and for each group we developed an individual therapeutic management. This management is based not only on the clinical effect of the drug, but is also supported by objective indicators (dynamics of infliximab levels and antibodies to infliximab in the serum). We have been following this management at our department since January 2013, and therefore each decision to modify or change the treatment is justified and therefore legitimate.

Methods

Patients

25 patients (20 men, 5 women) were enrolled in the clinical trial of...
infliximab in patients with chronic plaque psoriasis treated for at least 22 weeks (range 22-342 weeks). 4 patients also suffered from psoriatic arthritis. 5 patients were receiving adjuvant immunosuppressive therapy in addition to infliximab. One of these patients received methotrexate from the beginning of treatment with infliximab due to psoriatic arthritis and 4 patients had this treatment added due to insufficient effect. Ten patients did not have any biological therapy prior to the treatment with infliximab. Six patients had received efalizumab prior to infliximab, 1 patient ustekinumab, 6 patients etanercept, 1 patient adalimumab and 1 patient had received two biologicals (etanercept and adalimumab) prior to infliximab. Infliximab was administered at a dose of 5 mg/kg in week 0, 2, 6 and then every 8 weeks. The response to treatment was well defined at the time of examination and did not change (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions) and 1 patient (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions) and 1 patient (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions) and 1 patient (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions) and 1 patient (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions) and 1 patient (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions).

Measurement of clinical severity

Patients were divided into 3 groups according to clinical effect at the time of study. The responders had a good response to the treatment (all achieved at least PASI90), were completely or almost completely without symptoms (PASI 0-2.7) during the whole maintenance period. In partial responders, the effect of treatment was good only during the first weeks of the maintenance interval. In the last weeks a worsening of lesions always occurred, but after the infusion, antibodies to infliximab in week 8 (always before administering the infusion), antibodies to infliximab in week 8 (always before administering the infusion).

Results

Clinical efficacy of infliximab

Based on the clinical efficacy, 17 out of 25 patients were responders (clear or almost clear), 7 patients were partial responders (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions) and 1 patient (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions) and 1 patient (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions) and 1 patient (after infusion they were clear or almost clear, but in the final weeks there occurred a gradual worsening of their psoriatic lesions).
Figure 1: Protocol of sample collection during one maintenance interval – plasma levels of infliximab (IFX) and antibodies to infliximab (ATI). Sample collection in week 0 and 8 was always before administering the infusion.

Table 2: Dynamics of IFX levels and the presence of antibodies to infliximab in serum of patients with psoriasis treated with infliximab. IFX0–week 0., IFX2–week 2., IFX4–week 4., IFX6–week 6., IFX7–week 7., IFX8–week 8., IFX in ug/ml, ATI in IU/ml.
The responders did not produce antibodies to infliximab (17 patients). The level of infliximab in week 0 was never zero. The average value was 1.90 μg/ml (range 0.40 to 3.88 μg/ml). In week 2, the highest (so-called peak) infliximab concentrations were recorded at 11.64 μg/ml (range 5.25 to 27.67 μg/ml). Infliximab levels were gradually decreasing from week 2 until week 8, when just before the next infusion, they again were never zero. The mean values were 1.38 μg/ml (range 0.61 to 4.04 μg/ml). The dynamics of IFX levels in responders is shown in Figure 2a.

Partial responders may or may not produce antibodies against infliximab. We named those who produced antibodies as non-responders with production of antibodies. Those who did not form antibodies were labeled as responders with a shortened period of efficacy.

In our group there were only two responders with a shortened period of efficacy. Neither of them produced antibodies. The level of IFX in week 0 was zero or nearly zero. In week 2, the highest concentrations of infliximab were recorded. However, this peak was much lower compared to the peak value of responders (one patient 2.20 μg/ml and the second 1.92 μg/ml). Infliximab levels were gradually decreasing from week 2 until week 8, when they reached zero or nearly zero values again. The dynamics of IFX levels in responders with shortened period of efficacy is shown in Figure 2b.

All non-responders with production of antibodies produced antibodies against IFX (5 patients). We recorded not only the presence of antibodies but also their exact titer. The level of IFX in week 0 was always zero. In week 2, the highest concentrations of infliximab were recorded. However, this peak (3.07 μg/ml, range 2.47 to 3.48 μg/ml) was much lower than the peak value in responders and was comparable to that seen in responders with shortened period of efficacy. From week 2, infliximab levels sharply decreased down to the value of zero.

Dynamics of infliximab levels and detection of antibodies to infliximab

Infliximab levels and antibodies to infliximab in responders, partial responders and non-responders during the maintenance interval are listed in Table 2.
Depending on the amount of antibodies, these zero values were reached in week 6, 7 or 8. In patient no. 18, ATI titer was 41.553 IU/ml and zero infliximab level in week 8. In patient no. 19, infliximab level was zero in week 7 (ATI 504.243) and in the remaining three patients (no. 20, 21, 22) the zero infliximab level was reached as early as in week 6 (ATI respectively 169.771, 1270.963, 628.111). The dynamics of IFX levels in non-responders with production of antibodies is shown in Figure 2c.

The group of non-responders who did not produce antibodies was called non-responders without production of antibodies. This included only one female patient who did not respond to the treatment with infliximab at all. She did not produce antibodies to IFX and the dynamics of IFX levels was comparable with the dynamics of the levels in responders (Figure 2d).

**Proposed management of infliximab treatment based on clinical efficacy, dynamics of infliximab levels and detection of antibodies to infliximab**

Based on these results, we found that we are able to develop therapeutic management schemes for individual groups of patients according to clinical efficacy, dynamics of ATI and IFX levels.

**Group 1:** Responders: Patients belonging to this group are without lesions or almost without lesions (clear or almost clear) during the entire maintenance interval. Their residual (trough) IFX levels (in week 0 and 8) is never zero. They are characterized by high levels of IFX in week 2 (usually between 4-5 ug/ml). The higher is the value, the greater is the likelihood that the effect of treatment will be good. Responders do not produce ATI. Recommendation: Continue the treatment with infliximab without changes.

**Group 2:** Responders with shortened period of efficacy: Patients belonging to this group show no or almost no lesions after the infusion. At the end of the maintenance interval, a gradual deterioration of existing lesions occurs or there is an occurrence of new lesions. The residual level of IFX in week 0 and 8 is zero or only just above zero. Low peak of infliximab level in week 2 is characteristic. Responders with shortened period of efficacy do not produce ATI. Recommendation: Reduce the interval to 6 weeks. The effect of the reduced interval in responders with shortened period of efficacy compared to the initial 8-week interval is shown in Figure 3 (patient no. 24). After switching to 6-week intervals, the patient became a very good responder and has been completely without symptoms.

**Group 3:** Non-responders with production of antibodies: Patients belonging to this group show no or almost no lesions after the infusion but later, only a partial improvement of psoriatic lesions can be observed. Since the mid or rather towards the end of the maintenance interval, there is a gradual progression of the initial lesions or formation of new lesions. Antibodies produced by this group of patients are responsible not only for the insufficient effect of treatment, but also for the hypertensive infusion reactions, which these patients may experience. The trough level of IFX in week 0 and 8 is always zero. Peak in week 2 is very low and depends on the amount of antibodies produced by the patient (the more antibodies, the lower is this peak).
At the same time, the lower is the concentration of IFX in week 2, the sooner this concentration reaches the value of zero. Recommendation: First, add MTX to the treatment (7.5-15 mg/week) and continue with the 8-week interval. The effect of treatment after the addition of MTX in patient no. 20 compared to the condition before the addition of MTX is shown in Figure 4. If the addition of MTX does not help sufficiently, continue the treatment with MTX and reduce the interval to 6 weeks. If even reducing the interval does not help, it is appropriate to modify the biologic therapy, either for a biological with the same mechanism of action (etanercept, adalimumab) or with a different mechanism of action (ustekinumab). If we change infliximab for a drug with the same mechanism of action, etanercept is preferable since the potential production of antibodies to etanercept is not associated with a decrease in the effect (antibodies to etanercept are not neutralizing). If the treatment with etanercept is initiated, the use of MTX may be discontinued. However, if the treatment shifts to adalimumab, the MTX treatment should continue because the results of several studies suggest that patients producing antibodies to infliximab are more likely to develop antibodies against adalimumab and vice versa. If we shift to the drug with a different mechanism of action (ustekinumab) we can (but do not have to) discontinue using MTX. There are some data from the clinical practice on determining the presence of antibodies to ustekinumab. The results of the study PHOENIX show possible formation of neutralizing antibodies against ustekinumab. Their incidence was observed only in 4.9% of study patients and usually only in low titers. Probably also for this reason their presence has not been defined as a predictor of insufficient response [1,2]. However, continuing the use of MTX when switching from infliximab to ustekinumab could prevent a possible formation of antibodies.

**Group 4: Non-responders without production of antibodies:** Infusion of infliximab has no or only a minimal effect on psoriatic lesions. The residual levels of IFX in week 0 and 8 are never zero. Antibodies against infliximab are not produced. The dynamics of IFX levels is identical to the dynamics of responders with the difference that despite adequate therapeutic levels of IFX, there is a lack of treatment effect. Recommendation: Change biological treatment for a drug with a different mechanism of action (ustekinumab).

**Discussion**

Treatment of psoriasis with infliximab is effective and relatively safe. Its advantages are weight-based dosing, the possibility to reduce the interval or to increase the dose, the very well set up induction phase of treatment and the intravenous administration. The disadvantage is the occurrence of infusion reactions and the secondary treatment failure – in both cases often caused by the production of antibodies to infliximab. Another disadvantage is a relatively high cost of treatment, especially in patients with higher body weight. Therefore, it is very important to have objective indicators of treatment efficacy. The first indicator is the clinical picture. In case of responders, this indicator is sufficient. However, the problem may be with the patients in whom the treatment effect declines with time (secondary non-responders) or there is a lack of treatment effect (primary non-responders). In the case of non-response it is important to find the objective reason for therapeutic failure. One reason may be the production of antibodies to infliximab. Antibodies form immune complexes with infliximab and reduce the concentration of the medication to subtherapeutic or even zero values. The second reason of inadequate response may be an accelerated medication metabolism (e.g. its faster degradation or faster elimination). The third reason could be genetic predisposition to increased production of TNFα (e.g. TNF2 polymorphism). The next reason could be “cytokine booster” in the obese patients. In this type of patients the abdominal white adipose tissue produces adipokines that could raise the production of TNFα. An insufficient dose of medication relative to the weight of the patient could be another possible reason of the treatment failure. The last reason may be the treatment aimed at the wrong target cytokine (TNFα), which probably does not play a major role in the pathogenesis of psoriasis in some patients. Correct identification of the cause of treatment failure may on one hand prevent premature shift from one treatment to another, and on the other hand prevent unnecessary duration of the treatment. So this identification may help to decide on further therapeutic approach.

In our work we focused on observing the dynamics of IFX levels in patients with psoriasis treated for at least 22 weeks (mostly for more than one year). At this time, we already knew if the patient was a responder, partial responder or non-responder. Patients with infusion reactions were excluded from the study since the majority of infusion reactions occurred in the first year of treatment and therefore their dynamics were not observed. To our knowledge, this is the first work dealing with monitoring the dynamics of IFX levels in the serum of patients with psoriasis. Based on the results obtained and the presence or absence of antibodies to IFX, patients were divided into four groups – responders, responders with shortened period of efficacy, non-responders with production of antibodies and non-responders without production of antibodies.

None of the responders in our study produced antibodies. IFX levels in week 0 and 8 were never zero. The average trough level in our patients was 1.90 μg/ml (range 0.40-3.88 μg/ml) and 1.38 (range 0.61-4.04) respectively. It is higher than Takahashi et al. [3] published recently in their study of 20 patients treated with infliximab. He found that the minimum trough level of infliximab in good responders was 0.92 μg/ml. Similar to us, the Japanese authors used diagnostic kits by Matriks Biotec. A different result is probably given by the fact that the Japanese authors defined a good responder as a patient who had achieved an improvement of more than 75% (PASI75), while in our study we define responders as patients who have achieved at least 90% improvement (PAS90, clear or almost clear). Most of our responders were completely without symptoms. Torii and Nakagawa presented data on 40 patients treated with infliximab [4]. They found that when the patients with psoriasis had a residual concentration of infliximab in week 62 between 0.1 and 1 μg/ml, then 71.4% of patients reached PASI75 and if this level was between 1 and 10 μg/ml, then as many as 95.7% of patients reached PASI75. Based on our and Japanese results, it appears that the minimum trough level of infliximab for the treatment of psoriasis could be 1 μg/ml and the higher this value is, the higher is the probability that the patient will be a good responder. The peak value of IFX levels in week 2 in our patients was high – mean value of 11.64 μg/ml (range 5.25-27.67 μg/ml). This peak value of IFX was followed by a gradual decrease in the level of IFX from week 2 up to week 8. As we have mentioned above, none of the responders in our group produced antibodies. In six cases, however, a minimal but only transient positivity of antibodies (less than 10 IU/ml) were detected. The closest repeated measure was negative in all these patients. This so-called false positivity may be associated with the presence of other antibodies, high values of rheumatoid factor, and probably interference with serum level of infliximab [2]. The possibility of false positivity is also confirmed by the fact that a serum of one patient treated with etanercept was mistakenly mixed among the sera examined and there was also detected a minimum amount of antibodies to infliximab (0.869 IU/ml) and that is even despite the fact that the patient was never detected a minimum amount of antibodies to infliximab.
receiving any other biological therapy (and thus not even infliximab) besides the current treatment with etanercept. This finding confirms the previous theories that there are patients who produce antibodies and have a good clinical response. In their case, however, we are dealing with the above mentioned false positivity. So it is important not only to determine the presence of antibodies, but also their amount (titer). If the level of antibodies is only minimal, the examination should be repeated. If the repeated sample is negative, it was a false positivity. If the amount of antibodies increases, the patient produces antibodies against infliximab. Taking a blood sample for antibodies and IFX should always be done prior to the infusion, never after. During the infusion, the existing antibodies bind to the infliximab incorporated in the serum and form immune complexes. The antibodies in these immune complexes cannot be detected by ELISA examination and for this reason the level of circulating antibodies is significantly lower compared to the level prior to the infusion. As an example we mention a patient with hidradenitis suppurativa treated with infliximab. Prior to the infusion, the value of ATI was 1119.42 IU/ml but 30 minutes after the infusion, there was a decrease to 3.625 IU/ml.

Responders with a shortened period of efficacy do not produce antibodies. After the infusion, these patients are almost without symptoms or there is a significant improvement of clinical symptoms. In the last 1-2 weeks (rarely sooner) the psoriatic lesions begin to deteriorate again. The residual levels in week 0 and 8 are nearly zero or just above zero. The peak in week 2 is minimal. Because of the fact that patients do not produce antibodies, we have to search for the reason of insufficient levels of IFX elsewhere. The possible reason may be one of the following: accelerated drug metabolism or accelerated drug elimination, genetic factors, overproduction of TNFα by white adipose tissue in obese patients or insufficient dosage based on the weight of the patient. With regular monitoring of weight, the latter situation should not occur. The problem, however, could be in “borderline” patients whose weight is just below the borderline dividing the number of ampules (e.g. a patient weighing 98 kg will not benefit from a dose of 500 mg, but may benefit from a dose of 600 mg of infliximab). TNFα polymorphism can also play an important role. It was found that in some patients the TNF2 polymorphism (allele A at position -308) was associated with a several times higher production of TNFα and with some patients the TNF2 polymorphism (allele A at position -308) was reason, administration of MTX is not discontinued. In the literature, there is information that reducing the interval to 6 weeks or increasing the dose may paradoxically induce immunological tolerance and reduce the amount of ATI [9,17]. Plasencia et al. report the decrease in production of ATI in as many as 50% of patients with spondylitis after reducing the interval to 6 weeks [17]. A problem may occur in patients who cannot be administered methotrexate (hepatopathy, cytopenia in the past or other serious side effects). In that case, azathioprine can be added to the treatment (however not used in the treatment of psoriasis), systemic corticosteroids or, based on the above mentioned data, we could increase the dose or reduce the interval to 6 weeks. In the literature, the effect of systemic corticosteroids on the production of antibodies is controversial [11]. The most experience is with the treatment of gastroenterological patients with Crohn’s disease. According to Farrell [12], intravenous hydrocortisone premedication reduces the concentration of ATI but will not prevent the production of antibodies. Adding MTX to the treatment will reduce or even inhibit the production of antibodies, thereby increasing the effectiveness of
infliximab. So it is important to add MTX in time when the antibody levels are still not high and there is no risk of infusion reactions. From our experience, we administer MTX once we record the level of ATI above 100 IU/ml, or even sooner, if the production of antibodies is associated with a decline in effect in the final week. The sooner MTX is added, the greater is the chance that the production of antibodies will stop completely. If, despite the addition of MTX, there is no sufficient improvement in symptoms and not sufficient quantities of residual IFX levels, MTX treatment is continued and the interval reduced to 6 weeks. In case it does not work (which usually occurs only in cases where the production of antibodies is detected very late and their titer is already very high) or if the patient is no longer able to take MTX because of the side effects or the dose of MTX has to be reduced and this reduced dose may no longer be sufficient for the suppression of antibody production, there follows a change in biological treatment either for a drug with the same mechanism of action (adalimumab, etanercept) or with a different mechanism of action (ustekinumab). When switching to a medication with the same mechanism of action, the priority should be given to etanercept since there exists information about a greater risk of the production of antibodies when switching from one therapeutic monoclonal antibody to another (infliximab, adalimumab) than switching from monoclonal antibody to a fusion protein (etanercept) [19-21]. Moreover, antibodies to etanercept are not neutralizing and thus not responsible for the loss of effectiveness. For this reason, when switching from infliximab to etanercept, it is not necessary to continue with MTX. On the other hand, when switching to adalimumab, it is recommended to continue with the adjuvant treatment with MTX to prevent a possible production of neutralizing antibodies to adalimumab. When switching from infliximab to ustekinumab, treatment with MTX may (but does not have to) continue. Ustekinumab is a monoclonal antibody to which neutralizing antibodies are also produced, but according to the studies - only with low titers, and therefore should not affect the effectiveness of treatment [1,19,22].

The last group of patients is non-responders without the production of antibodies. The dynamics of IFX is the same as in responders. During the entire maintenance interval IFX is sufficient and trough levels in week 0 and 8 are never zero. On the contrary, they are sufficiently high. This type of patients does not produce antibodies. It follows from the aforementioned that in these patients, TNFα will probably not be the major cytokine responsible for the formation of psoriatic lesions and therefore infliximab treatment should be discontinued and switched to the drug with a different mechanism of action (e.g. ustekinumab).

At our department, we manage infliximab treatment in psoriatic patients based on the clinical picture, ATI and IFX levels. The current protocol used in the daily practice is shown in Figure 5. Levels of IFX are examined for the first time in week 2. Antibodies to infliximab and trough level of infliximab are examined in week 6, 14, 22 and 54. If the patient does not produce antibodies and has a sufficient level of IFX as reflected by the clinical response, he is classified as a responder. Control samples of ATI and IFX levels are taken just once a year or whenever necessary with a deteriorating condition. For non-responders and partial responders, the basic protocol scheme is used up to week 22 and then whenever necessary. Based on the obtained results, the patient is classified as a responder with shortened period of efficacy, non-responder with production of antibodies or non-responder without production of antibodies. The suggested management of infliximab treated patients for clinical use based on clinical picture, ATI and IFX trough level is shown in Table 3.

**Conclusion**

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<th>IFX</th>
<th>Responders</th>
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<th>Non-responders with production of antibodies</th>
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<td>ATI</td>
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**Clinical efficacy**
- good response
- shortened period of efficacy
- shortened period of efficacy, later no response
- no response

**Recommendation**
- continue in the treatment without changes
- reduce maintenance interval to 6 weeks
- add MTX
- reduce maintenance interval to 6 weeks
- change biological ETA–ADA or UST
- change biological - UST

**Table 3:** Proposed therapeutic management based on clinical efficacy, trough levels of IFX and ATI. ADA–adalimumab, ETA–etanercept, UST–ustekinumab, MTX–methotrexate.
In this paper we have shown that ATI and IFX levels are very important in clinical practice in psoriatic patients treated with infliximab. According to dynamics of IFX during the maintenance interval in patients with well-defined response to treatment and the presence or absence of ATI, the patients could be divided into four groups and a specific therapeutic management can be created for each group. We have been successfully following this management for more than one year. Based on the objective (clinical and laboratory) indicators, we can determine not only the efficacy, but also the cause of insufficient effect of infliximab treatment. Specifying the cause of insufficient treatment effect enables us to make rational therapeutic decisions, which are of benefit not only for the patient, but also for the insurance company. As our group of patients is very small, there will be the need for further studies on a larger cohort of patients, which would confirm our conclusions and would search for the cause of low concentration of infliximab in responders with shortened period of efficacy.

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References