

Hard-to-treat psoriasis in a child developing neutralizing anti-drug antibodies against adalimumab during *Streptococcus pyogenes* throat infection: a case report

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Abstract

We report a case of a child with severe psoriasis vulgaris that developed neutralizing anti-drug antibodies against the biologic agent adalimumab 3 months after the first administration of the drug during *Streptococcus pyogenes* infection of the throat. After replacement of biologic agent, she was unsuccessfully treated with etanercept. Treatment with ustekinumab was the last option and initially it also appeared ineffective, but as we shortened the interval and doubled the dosage our patient's skin condition finally improved.

Keywords: psoriasis, child, biological therapy, antidrug antibodies, adalimumab, *Streptococcus pyogenes*

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Case report

An 8-year-old girl, who weighed 52 kg at the time, was admitted to our in-patient clinic due to exacerbation of psoriasis vulgaris appearing as non-pruritic, erythematous, scaly plaques, which first appeared at 4 years of age. Earlier treatment included local corticosteroids and narrow-band UVB 311 phototherapy, but no long-term remission of the disease was achieved. In her family history, her grandfather and her brother had both been diagnosed with psoriasis. Other than this disease and being overweight, she was completely healthy.

On first admission she presented with multiple well-demarcated psoriasiform plaques and papules on the forehead and across the trunk and limbs, and her scalp was covered with extensive erythematous plaques with white scales. Nail pitting was present, but the joints were not affected. Her Psoriasis Area and Severity Index (PASI) score on admission was 45. She was treated with corticosteroid cream, keratolytic shampoo, and oil for the scalp, and systemic therapy with methotrexate at a dose of 12.5 mg weekly was started. While receiving systemic immunosuppressant therapy, she underwent frequent regular checkups and tests, but only partial regression of skin lesions was noted. Therefore, methotrexate was discontinued after 2 years of systemic therapy.

Due to the moderate to severe form of psoriasis, we decided to prescribe biological therapy. Based on the registration of biologics according to the age of the patient, we decided to start treatment with an inhibitor of TNF- α , adalimumab. She was admitted to the hospital for the first subcutaneous application of the drug, and her PASI score was 10.7. At age 10 she weighed 69 kg and was 161 cm tall, and her total body mass index (BMI) was 26.6. First a dose of 80 mg s.c. was administered, followed by 40 mg every 2 weeks. At the examination after 12 weeks (Figs. 1–2), despite regular administration of adalimumab s.c. injections, generalized exacerbation of psoriasis was seen. With a PASI score of 20.6, laboratory tests showed severely elevated antibodies against adalimumab (above 1,000 ng/ml) and lowered blood concentration (below

0.50 μ g/ml) of adalimumab. During her adalimumab treatment she underwent 10 days of antibiotic treatment with penicillin due to a positive throat swab and isolated beta-hemolytic streptococci (*Streptococcus pyogenes*). An isolated bacterial infection could be the trigger for worsening of the disease, but due to the antibodies detected we concluded that neutralizing anti-drug antibodies (ADAs) had developed, which was the real cause of worsening of the psoriasis, and so we switched the biological therapy for the only approved biologic left for the girl's age: etanercept. Based on her body weight, an adult dosage was prescribed, 50 mg twice weekly for the first 12 weeks. Her clinical progress was evaluated again after 10 weeks, when we realized that the therapy with etanercept was yet another unsuccessful option. Dermatological examination revealed new erythematous plaques, and at that time her PASI score was 19.4 and Family Dermatology Life Quality Index (FDLQI) 13. The next possible treatment left for children and adolescents was the biological agent ustekinumab; however, at that time its use was limited to children over 12, and our patient was only 10.5 years old. Nevertheless, because this was the only possible therapy left to improve our patient's quality of life, after receiving her parents' consent, a medical council of pediatric dermatologists decided to start treatment with ustekinumab. She had a PASI score of 12.3 when ustekinumab 45 mg s.c. was started. Initially it seemed successful, but in the following months the skin condition deteriorated again. Because she weighed 85 kg, we decided to increase the dose of ustekinumab to 90 mg s.c. every 12 weeks and we reduced the dosing interval from 12 to 8 weeks. At the next examination the psoriasis was noticeably improved with a PASI score of 3.3, which was the lowest in recent years.

For the following admissions we advised her to continue with ustekinumab 90 mg s.c. every 12 weeks. At the last check-up she was 12 years old, she weighed 92 kg, her height was 179 cm with a BMI of 29, and her PASI was 2.8 (Figs. 3–5). Although she was overweight, she did not have any associated metabolic diseases, and her blood pressure, lipids, and blood sugar were within normal ranges.

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Figures 1,2 | A 10-year-old girl with generalized psoriasis 4 months after the introduction of adalimumab.

Discussion

We followed the treatment of a girl suffering from severe psoriasis from age four. On her first admission to children's ward at our clinic, we introduced systemic treatment with methotrexate, one of the most commonly used conventional systemic therapies in treating psoriasis in adults. According to new guidelines for the treatment of children and adolescents with psoriasis, methotrexate is also considered a safe and effective medicine in this age group and should be prescribed prior to the initiation of biological therapy (5, 6).

For our patient, methotrexate was discontinued after 2 years due to a lack of sufficient and long-lasting improvement of her skin condition. Because she had a severe form of psoriasis, biological therapy was the next treatment of choice. In standard protocol, a combination of biological therapy with methotrexate is not suggested, but concomitant methotrexate has been associated with less antibody formation (7). The mechanism behind it is still unknown, and further investigation is needed to determine its utility (1). Biologics such as TNF- α inhibitors are highly effective for treating severe psoriasis, and today an increasing number of patients benefit from them. They act on the specific therapeutic



Figures 3-5 | A 12-year-old girl 1 year after introducing ustekinumab.

target and are therefore more efficacious and tolerable than conventional systemic therapies such as cyclosporine and methotrexate (3). However, there are instances in which the patient fails to show any response to the drug or the drug appears to lose its efficacy in the course of treatment.

Our patient underwent treatment with three different biologic agents. An increasing number of studies support changing one type of biologic for another if the first fails to produce the desired results (1). Adalimumab showed no efficacy, and it even worsened the condition of the disease and the patient's blood results showed severely elevated antibodies against adalimumab (over

1,000). High concentrations of ADAs are associated with undetectable adalimumab levels as well as a poor clinical outcome (3). Consequently, her adalimumab concentration blood levels were below 0.5 µg/ml. Adalimumab trough concentration above 5.0 µg/ml has been found to be sufficient to obtain a good response (3).

Formation of antibodies has been correlated with patients that had higher disease activity, longer duration, and more severe disease together with increased C-reactive protein (CRP) (1). Neutralizing antibodies interfere with the biologic agent's binding activity, leading to a diminished clinical response. The greatest chance of first-time ADA development is during the first 24 weeks

of treatment (8), and studies suggest that adalimumab levels at 4 weeks predict treatment response at 6 months (9). Furthermore, in those with low levels of adalimumab at week 4, a change of biologic agent is advised (7). It has been shown that ADA formation is lower in rheumatoid arthritis and psoriasis patients receiving higher doses (3, 7). On the other hand, in patients with psoriasis undergoing long-term treatment with adalimumab and etanercept, ADAs and anti-TNF levels are not related to clinical effectiveness (10).

Our patient experienced *S. pyogenes* infection of the throat during her adalimumab treatment. Increased CRP, which is seen in bacterial infections, can correlate with formation of antibodies, and the immunological activity in young patients may also affect the productivity of the antibodies (7), and so the bacterial throat infection could be a potential reason for the development of ADAs.

Etanercept was introduced as a second biologic and was yet another unsuccessful attempt because it did not cause any improvement of the psoriasis in 12 weeks. On the other hand, etanercept efficacy is not influenced by plasma drug levels and forma-

tion of ADAs (4). Some studies indicate that methotrexate should be considered for patients that are about to be treated with their second TNF inhibitor after developing antibodies (3), but other studies have shown it does not reduce ADA formation (8). The last option for our patient was interleukin-12 and interleukin-23 (IL-12/IL-23) inhibitor ustekinumab, which (with later adjustments of dosage and administration frequency) finally resulted in favorable clinical progress. Through the years of different treatment, we managed to lower the patient's PASI index from 45 to 3.3, proving we may have found the right combination of dosage and administration frequency for our patient.

The presence of ADAs against biological agents in children is rarely described in the literature. To our knowledge, our case is the only confirmed case of a child with psoriasis developing ADAs in Slovenia.

So far we are following only a few children with moderate to severe psoriasis being treated with adalimumab and other biologics, and their clinical progress mostly shows very encouraging results.

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