GMN: Georgian Medical News

GEORGIAN MEDICAL NEWS

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LOSS OF EFFICACY OF ADALIMUMAB IN HIDRADENITIS SUPPURATIVA: FOCUS ON ALTERNATIVES

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Abstract.

The loss of efficacy of adalimumab, one of the most commonly used biologics for the treatment of hidradenitis suppurativa/acne inversa, is not news to the scientific community, and it should be noted that the number of cases not responding to this agent has been progressively increasing in recent years.

We present a 45-year-old patient with hidradenitis suppurativa/acne inversa (Hurley II-III) with a complaint duration of 3 years who has been on adalimumab 40 mg weekly for 9 months. The lack of improvement in the clinical condition as well as the progression of the disease within the ongoing biologic therapy led to the need for repeated hospitalizations and the additional introduction of intravenous treatment with a regimen of antibiotics (Ertapenem, Metronizadol, Ceftriaxone), zinc, colchicine, and pain relievers.

During these hospitalizations, a partial improvement was found, which was not durable and required the parallel administration of antibiotics, colchicine and zinc in combination with adalimumab in an outpatient regimen.

Several attempts at surgical treatment/incision in non-specialized units were also made, and these too remained generally unsuccessful or with a nondurable, unsatisfactory clinical outcome.

Due to the subsequent consecutive worsening of the symptomatology, the patient was admitted for evaluation of the clinical condition and optimization of treatment. Surgical treatment was performed by surgical deroofing under general anaesthesia, concurrent with discontinuation of adalimumab/antibiotic application and long-term remission was achieved.

Surgical deroofing has also been shown to be an effective therapeutic option in the loss/lack of efficacy of adalimumab in patients with hidradenitis suppurativa (Hurley II-III).

In the case of therapeutic resistance or worsening of symptomatology in patients with acne inversa within adalimumab therapy, other advanced alternatives such as golimumab, anakinra, etanercept are available.

The efficacy of these second-line agents is also questionable due to the development of resistance to them as well, which in turn necessitates the frequent switch to third-line agents such as: Ustekinumab, Tildarkizumab, Certolizumab or Ixekizumab. The future will show to what extent this "trust" could be justified and whether in practice the surgical approach will once again displace the so-called "modern options" as the reasonable next basic and reliable alternative.

The disadvantage of modern biological therapy is mainly due to the loss of efficacy/development of resistance over time, multiple side effects and frequent recurrence after discontinuation of treatment. In contrast, in the case of specific, stage-oriented, specialized surgical treatment of hidradenitis suppurativa/ acne inversa, in the form of surgical deroofing, for example, the results are long-lasting and in the case of recurrences: the latter are much more easily managed by dermatosurgery/surgery again. The effect achieved after this type of manipulation is essential for the patients' quality of life and guarantees to a large extent also prevention of the development of keratinocyte tumours in the areas affected by chronic inflammation. Precisely because of the aforementioned facts, in a serious number of patients this type of treatment could be considered as a priority. The rethinking of the guideline and the staging of surgical modalities as first-line therapy could, in a serious number of patients, have a positive effect. Swap for surgery seems to be a good alternative.

Key words. Adalimumab, surgical deroofing, acne inversa, hidradenitis suppurativa, Hurley II-III, undermining surgery.

Introduction.

Although, until recently, suppurative hidradenitis (as a clinical mono manifestation or in combination with pyoderma gangrenosum) has been successfully treated with adalimumab [1], there is now an avalanche of evidence that points to a loss of efficacy of the drug. This, in turn, necessitates a change in the therapeutic regimen and a switch to other biologics such as 1) Ixekizumab [2], 2) Brodalumab [3], and a number of others. Unfortunately, a number of these are not available as basic therapy or even as alternatives in certain geographic latitudes.

On the other hand, the side effects of adalimumab are also not infrequently a reason to stop the medication in question, as it could (in certain cases) seriously endanger the health of patients [4].

Severe forms of hidradenitis suppurativa are no exception in this respect- when adalimumab medication is stopped for a short time, a progression to more severe forms such as Hurley II-III has been observed, which cannot be managed either medically or surgically [5]. This necessitates a rethinking of the therapeutic strategy and a search for new alternatives.

We present a 45-year-old patient, who has been on adalimumab therapy for 9 months, with a lack of efficacy of the biologic and disease progression during this therapy. This prompted his repeated hospitalization, during which he also required the introduction of concurrent antibiotic therapy with metronidazole and ertapenem regimen (in combination with colchicine), again the improvement was short-lived and unsatisfactory.

The patient was referred for surgical treatment, and after surgical deroofing a durable remission was achieved, and adalimumab therapy was permanently discontinued.

Case report.

A 45-year-old male came to the dermatology department with primary complaints of painful, erythematous, secreting nodules, cicatrices and fistulas with exudation located in both axillary
and inguinal regions. Complaints began 3 years ago with the spontaneous appearance of painful, erythematous nodules in the axillary folds, later appearing in the inguinal folds too. Pain, febrility up to 38.4 and general debility.

The patient had four previous hospitalizations for hidradenitis suppurativa.

Multiple surgical incisions and the subsequent elimination of pus were performed in the past in the coccyx and axillae areas with a temporary effect.

The last surgical intervention in the form of incision was in January 2022 during his third hospitalization for the lesions located in the axillary regions, the effect is again short-lived and requires temporary hospitalization.

Systemic therapy during the years with the following medications were carried out-different antibiotic courses with:

1) Within one of the hospitalizations: Ertapenem 1g daily intravenously in combination with Ceftriaxone 2 g daily intravenously and metronidazole 500 mg twice daily; colchicum disp 0.5 mg twice daily, ketotifen 1 mg twice daily, zinc gluconate 30 mg two tablets three times a day for 10 days. Local treatment was carried out with wound gels twice daily: iodinated povidone 10% solution, resorcinol 15 % cream, chlorhexidine gluconate 4%.

2) Within another hospitalization, systemic antibiotic therapy included the following regimen: Ceftriaxone 2g daily i.v. in combination with Metronidazole 500 mg twice daily intravenously; Zinc gluconate 15 mg 3 times daily per os; Fluconazole 50 mg once daily for 1-2 months, silymarin 90mg - 2 times one per day, Zn gluconate 15mg / 3 times daily two tablets.

In the outpatient setting, antibiotic treatment was continued with metronidazole 250 mg according to the following regimen: 2 times 2 tablets for one week, followed by 3 times 1 tablet (for one week), and the dose was subsequently changed to 2 times 1 tablet for 2 weeks, followed by 1 tablet for 3 months. Colchicine was continued on an outpatient basis according to the following schedule: twice daily at 0.5 mg for one month, with subsequent dose reduction to once daily. Ketotifen 1mg twice daily, fluconazole 50mg once daily for 1-2 months, silymarin 90mg - 2 times one per day, Zn gluconate 15mg / 3 times daily two tablets.

In parallel with this the patient was put on adalimumab for 9 months during his last hospitalization in 2023, with applications every week with 1 amp 40 mg administered subcutaneously.

Lack of therapeutic effect of adalimumab administration. Partial improvement of the condition after concomitant administration of combined antibiotic therapy under inpatient conditions, which resolves relatively quickly with antibiotic dose reduction in the outpatient setting.

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Outpatient therapy was continued again in combination with adalimumab on a schedule / 40 mg weekly / and did not lead to significant improvement: doxycycline 100 mg once daily for a month in combination with colchicine 0.5 mg and one tablet for a month, Silymarin 90 mg twice daily for a month, and zinc gluconate 15 mg : 3 times two tablets for a month.

The patient also had arterial hypertension for which he takes candesartan cilexetil/amldopine 16/5 mg once in the morning. No family history for dermatoses was reported. He reports drinking alcohol and smoking cigarettes.

The patient requested a physical examination and further therapeutic approach to be established.

Routine blood tests were performed, resulting without abnormalities.

The dermatological examination showed symmetric exanthema in the axillary folds; erythematous, inflammatory, and secreting nodules, aggregating into plaques, fistulas and postoperative cicatrixes in the axillary and inguinal areas (Figures 1 and 2). The patient’s hidradenitis suppurativa was staged as severe - Hurley 3, IHS4 score > 11.

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Several surgical excisions were planned to remove the lesional sites located in the inguinal and axillary regions. Significant improvement of the clinical picture was achieved, as 4 months after the operation the secretion from the affected areas was reduced by about 75-80%, clinically there were several single nodules with a slightly raised surface and significant less soreness to touch. General debility and febrile states are absent. A second surgical session is planned for definitive surgical repair of the suppurative nodules.

**Discussion.**

The lack or loss of effectiveness of biologics in patients with hidradenitis suppurativa is not new and dates back more than a decade [6]. In addition to adalimumab, ineffectiveness/loss of
efficacy or therapeutic resistance has also been observed after the administration of golimumab, anakinra and etanercept [6,7]. However, the lack or loss of efficacy of adalimumab is proving to be more than problematic, as a kind of credibility is being lost in the main biologic officially approved for the treatment of hidradenitis suppurativa/acute inversa, whose clinical efficacy was until recently estimated to be as high as 86.7% [8,9].

It is currently unclear whether switching to golimumab [10-12] or Ixekizumab [2] will remain as a durable alternative and adalimumab will be completely replaced. Another problem besides the lack or loss of effectiveness of adalimumab is the occurrence of paradoxical reactions that lead to: 1) the co-occurrence of plaque psoriasis and palmoplantar pustulosis/within the treatment of HS [13], 2) the manifestation of psoriasiform eruptions on the skin/within the treatment of HS [14], 3) psoriasiform reactions in combination with sacroiliitis/within the treatment of HS with adalimumab [15], 4) occurrence of hidradenitis suppurativa/within the treatment of Crohn's disease with adalimumab [16]. Side effects of the medication appear to be somewhat unpredictable. The future will tell whether confidence in both Tildarkizumab and Certolizumab will remain justified, although initial data on their efficacy in a limited number of patients with acute inversa are encouraging [17,18]. Similar data are available for the administration of ustekinumab [19].

Characteristic of the profile for shared advanced therapeutic options remain the following negatives 1) loss of efficacy of the drug within the ongoing treatment; 2) severe side effects that could accompany this treatment; 3) frequent worsening of clinical symptomatology after discontinuation of their administration; 4) neutropenia, infections, local reactions, systemic reactions. Similar should be the characteristics of long-term antibiotics and retinoids: immunity decline, development of resistance, hepatic and renal toxicity, ineffectiveness at the start of therapy. This is what necessitates a rethinking of the therapeutic strategy, namely: staging of certain surgical techniques to lead to long-term or lasting improvement of symptoms. Or to reduce the clinical symptomatology and lead to better susceptibility and disease control to the milder non-invasive options. In practice, an exacerbation of this disease after correctly performed surgical treatment is extremely rare. Surgical deroofing and elliptical excisions are a good opportunity to test this strategy in patients with Hurley I-III, and they often result in durable or long-term remissions [20,21]. Performing rotational and transpositional flaps under general anesthesia has also been shown to have long-lasting or permanent effects [22]. Subsequent close monitoring of these patients in the postoperative period is also crucial for prognosis.

Multiple incisions of inflammatory nodules in combination with systemic antibiotics performed in patients often do not have the expected therapeutic effect, similar to the patient we have shown in our publication. Specialized surgical approach such as deroofing, seems to be a wonderful option. Nevertheless, the evidence in world literature that loss of efficacy of adalimumab has been described in patients with Crohn's disease [23] as well as in those with rheumatoid arthritis [24] should not be ignored.

Strategies in the absence of such efficacy are generally always twofold: either switching to a drug in the same group (switch to another TNF alpha block) or switching to one with a radically different mechanism of action (swap/for another mechanism of action) [25]. However, both of these options: 1) do not insure patients against recurrent loss of efficacy-development of resistance, 2) often have serious side effects, and 3) after stopping them - a recurrence of symptomatology occurs, and this clinical picture could be often more difficult to manage than the initial one and requires in a high percentage of cases hospitalization of patients. According to recent evidence, even switching to so-called biosimilars is no guarantee of success and the loss of efficacy could be even more pronounced than with adalimumab, for example [26].

Therapeutic resistance to biologics in general could probably be at least temporarily overcome/avoided precisely by switching to a new form of basic or first-line treatment: surgical treatment in the form of surgical elliptical excisions, specific surgical deroofing, or more severe rotational/transpositional flaps tailored to the clinical findings and localization of the suppurative nodules and fistulas. Changing this algorithm in single patients (in favour of dermatologic surgery/surgery as first-line therapy followed by systemic antibiotic therapy, for example) is indicative that in a serious number of patients, systemic adalimumab administration is not necessary or could be minimized. Conducting several consecutive (surgical) interventions during well-defined periods and in the framework of interdisciplinary collaboration between dermatologists and surgeons is essential to achieve optimal results that spare patients the long and prolonged treatment with biologics and systemic antibiotics that gradually lose their effectiveness as the disease progresses (so-called tachyphylaxis). The new, strictly structured withdrawal of the disease activity by changing the initial approach and initiating the first line treatment by dermatosurgical/surgical one means could subsequently provide the opportunity for a subsequent significantly better therapeutic response in general, but also better susceptibility and disease control to the milder non-invasive options.

This, in turn, and in general, should have a sparing effect on patients’ organism in the long perspective. Changing the therapeutic algorithm as a move and in favour of invasive therapeutic options in these patients could in all likelihood prove decisive and profitable in the long course.

REFERENCES


