



Systemic adverse events in imiquimod use for cervical intraepithelial neoplasia – A case series

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ABSTRACT

Treatment for cervical intraepithelial neoplasia (CIN) often consists of an excisional procedure. However, less invasive treatment methods have been explored, such as topical treatment with imiquimod cream. Imiquimod has been proven to be effective in the regression of vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN). Previous studies have investigated the effect of imiquimod in CIN and showed well tolerated adverse effects. During a current study in the Netherlands, a number of adverse events have occurred. This case series presents a selection of these. Gynaecologists should be aware of the possible adverse effects of topical treatment with imiquimod cream.

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1. Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignancy. Treatment often consists of an excisional procedure with possibly a negative impact on subsequent pregnancies, as it is associated with a significantly higher risk of miscarriage [1]. To prevent these adverse effects, less invasive treatment methods have been explored. A possible non-invasive therapy for CIN is a toll-like receptor (TLR) 7 agonist: imiquimod.

Imiquimod cream has been proven to be effective in the regression of vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN) [2,3]. Both VIN and VAIN are HPV-related neoplasia and the pathophysiology is comparable to CIN. Previous studies have investigated the effect of imiquimod in CIN and showed the adverse effects to be well-tolerated [4,5]. Currently, a non-randomised study comparing the effectiveness of imiquimod treatment with large loop excision of the transformation zone (LLETZ) is being performed in the Netherlands (TOPIC-3) [6]. The patients were instructed to administer one sachet containing 12.5 mg of 5% imiquimod with a vaginal applicator three times weekly intravaginally. During this study, a number of adverse

events have occurred, in some cases severe enough for patients to discontinue treatment with imiquimod.

The purpose of this case series is to present the serious adverse events in patients who received imiquimod 5% cream intravaginally for cervical intraepithelial neoplasia (CIN 2–3). Gynaecologists should be aware of these adverse effects. In addition, a summary of prior research on adverse effects in CIN is provided. We obtained medical ethical approval as well as written consent from the patients described.

2. Patient Series

2.1. Case 1

A 79-year-old woman with myocardial infarction and anxiety disorder in her medical history was seen at the outpatient clinic with postmenopausal bleeding. During the workup, a cervical smear revealed atypical squamous metaplasia. Colposcopic and histological examination revealed a high-grade squamous intraepithelial lesion (HSIL). In preference to surgical intervention, the patient chose the imiquimod treatment. After three vaginal applications, with the last application 4 days earlier, the patient was hospitalised with general malaise, persisting nausea, mild diarrhoea, asymptomatic hyponatremia (Na^+ 126 mmol/L) and leukopenia (2.5/nL). Her C-reactive protein (CRP) level was <6.0 mg/L and her temperature was between 36.5 and 37 °C

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Table 1
Summary of three cases with adverse events.

| Case | Age | Bethesda system | Number of imiquimod applications | Adverse effects | Serious adverse events |
|------|-----|-----------------|----------------------------------|---|------------------------|
| 1 | 79 | LSIL | 3 | <ul style="list-style-type: none"> – Malaise – Persisting nausea – Mild diarrhoea – Asymptomatic hyponatremia – Leukopenia | Hospitalisation |
| 2 | 51 | HSIL | 18 | <ul style="list-style-type: none"> – Spontaneous headache – Light-headedness | Hospitalisation |
| 3 | 45 | HSIL | 12 | <ul style="list-style-type: none"> – Headache – Abdominal pain – Nausea – Fatigue – Fever – Erosion of the cornea | Corneal erosion |

LSIL = low-graded squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion.

during the hospitalisation. No local effects were mentioned by the patient. The imiquimod cream was discontinued as it was hypothesised that the cream was the cause of the clinical complaints. After three days, the patient was discharged fully recovered. She did not restart the imiquimod treatment.

2.2. Case 2

A 51-year-old woman with post-traumatic stress disorder, high blood pressure, hypercholesterolemia and spinal stenosis C5–C6 in her medical history was seen at the outpatient clinic with persistent vaginal bleeding after IUD insertion. During the workup, a cervical smear revealed a mild–moderate dysplasia. Colposcopic and histological examination showed HSIL. The patient did not want to experience the excisional procedure and therefore chose the imiquimod treatment. After 6 weeks of vaginal application of imiquimod, the patient was hospitalised with spontaneous headache and light-headedness. Her laboratory results showed a CRP of <6.0 mg/L, leukocytes of 8.2/nL and D-dimer of 0.32 mg/L. Imaging techniques and examination of the cerebral liquor did not explain her symptoms. No local effects were mentioned by the patient. The imiquimod treatment was discontinued. The patient was released from hospital the next day as the symptoms disappeared during the hospitalisation.

2.3. Case 3

A 45-year-old woman with a herpes simplex virus infection, breast reduction and caesarean section in her medical history presented at the outpatient clinic with an abnormal cervical smear detected by the national screening programme for cervical premalignancies.

Colposcopic and histological examination revealed HSIL and the patient chose the imiquimod treatment to prevent the excisional procedure. After 4 weeks of vaginal application of imiquimod, the gynaecologist decided to stop the treatment due to systemic adverse effects: headache, abdominal pain, nausea, fatigue, a temperature of 38.9 °C and a spontaneous erosion of the cornea. The patient reported vaginal discharge and vaginal bleeding a week before the appearance of the systemic effects. No laboratory tests were performed. Cultures were negative for microorganisms that could explain the erosion of the cornea. As it was hypothesised that the cream could be the cause of the complaints, the treatment was discontinued. Within 45 days, all complaints subsided and the patient recovered from the erosion of the cornea.

3. Discussion

We describe three cases of adverse events in women treated for HSIL with imiquimod, summarized in Table 1. However, in none of the patients were these adverse effects proven to be caused by imiquimod. The symptoms all disappeared after discontinuation of imiquimod. In a previous review, De Witte et al. showed a higher rate of adverse effects in imiquimod use compared with placebo; however, these adverse effects were less severe than in our study [7]. The most common and severe local and systemic effects reported in literature are summarized in Table 2.

Adverse effects of imiquimod treatment of H/LSIL lesions were previously reported by three authors. Firstly, the RCT performed by Grimm et al. established local and systemic adverse effects [4]. The authors concluded that the treatment was well tolerated without high-grade adverse effects. Vaginal suppositories were used for the application of the imiquimod cream by the patients themselves. Pachman et al. studied the cervical application of imiquimod [8]. A near syncopal event in one patient was described. However, this patient was not hospitalised and she continued treatment. The 50 mg of 5% imiquimod oil-in-water cream was applied directly to the ectocervix by the research nurse. A retrospective study was carried out by Lin et al.⁵ In their study, no patient discontinued the treatment due to adverse effects. In this study, the patients were instructed to apply 250 mg of 5% imiquimod cream using their fingers.

Based on these studies, the adverse effects of imiquimod seem well tolerated. The most common systemic adverse effects described in these studies were: headache, fever and/or fatigue and myalgia. With the exception of myalgia, these systemic adverse effects were also experienced by the patients described in our case series. However, general malaise, persisting nausea, mild diarrhoea, asymptomatic hyponatremia, leukopenia, light-headedness, abdominal pain, nausea and a spontaneous erosion of the cornea were not mentioned before.

The systemic adverse effects can be explained by the mechanism of action of the cream. Schön et al. detail how the major effect is caused by the agonistic activity towards TLR 7 and 8 and nuclear factor-kappa B (NF-kappa B) [9]. This activation induces the upregulation of pro-inflammatory cytokines and chemokines. A study performed by Nerurkar et al. established significant upregulation of

Table 2
Studies reporting systemic and local adverse effects in imiquimod treatment for cervical intraepithelial neoplasia.

| Study | Study design | Treatment | Adverse effects | | | | | | | | Serious adverse events | |
|--------------------|--------------|------------------------|--------------------------|---------|---------|---------|-----------------------|------------------|-----------------|-------------|------------------------|---------------|
| | | | Systemic adverse effects | | | | Local adverse effects | | | | | |
| | | | Head-ache | Fever | Fatigue | Myalgia | Vaginal discharge | Vaginal bleeding | Vulvar pruritus | Vulvar pain | | Vaginal edema |
| Grimm et al. [8] | RCT | Imiquimod group n = 30 | 25 (83) | 29 (97) | | 23 (77) | – | – | 28 (93) | | 16 (53) | No |
| | | Placebo group n = 29 | 6 (21) | 12 (34) | | 3 (10) | | | 11 (38) | | 3 (10) | |
| Pachman et al. [9] | PS | Imiquimod n = 28 | 7 (25) | 5 (18) | 13 (46) | 15 (54) | 9 (32) | 1 (4) | – | – | – | No |
| | | ST n = 28 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | | |
| Lin et al. [10] | RS | Entire cohort n = 72 | – | 3 (4) | 2 (3) | 1 (2) | 7 (10) | – | 3 (4) | 2 (3) | – | No |

RCT = randomised controlled trial; PS = prospective study; RS = retrospective study; ST = standard treatment.

pro-inflammatory cytokines and chemokines in a number of peripheral organs in mice exposed to imiquimod. Upregulation was detected in skin, liver, lungs and the brain [10]. An increase in cytokines and chemokines leads to activation of the T-helper (Th1) anti-tumoral cellular immune response. Therefore, it could well be that the systemic adverse effects were caused by the peripheral Th1 immune response induced by the imiquimod cream.

It could be argued that the patients described in the present case series should not have started the imiquimod treatment at all. The non-invasive treatment with imiquimod was initially developed to decrease the possibility of the negative impacts on subsequent pregnancies in women with a wish still to have children [11]. Women with no intention to become pregnant do not have to weigh the possible negative impacts and they should be advised to weigh the treatment and the adverse effects carefully. On the other hand, patients were allowed to choose a treatment arm in this study, for example to prevent LLETZ under general anaesthesia. Therefore, the imiquimod treatment in the described cases is justified by the patient's own choice of treatment.

Based on the primary studies, the adverse effects in imiquimod treatment for H/LSIL were well tolerated. However, during the current TOPIC-3 study, we witnessed two serious adverse events and mild/moderate adverse effects that could be due to imiquimod use. With this case series, we draw attention to the possibility of serious adverse events in imiquimod treatment, which are generally reversible. Monitoring patients during imiquimod use could reveal whether systemic adverse effects are more frequent in imiquimod users.

Contributors

Arnold-Jan Kruse conceived of the case series.

All authors were involved in the clinical study and contributed to the drafting and revision of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Ethical Approval

Ethical approval for the clinical study was granted by the medical ethics boards of the Catharina Hospital Eindhoven, Maastricht University Medical Centre, Erasmus Medical Centre Rotterdam.

Patient Consent

Patient consent was obtained from the three women described in this case series.

Provenance and Peer Review

This case report was peer reviewed.

References

- [1] M. Kyrgiou, A. Mitra, M. Arbyn, et al., Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis, *BMJ*. (2014) <https://doi.org/10.1136/bmj.g6192>.
- [2] S. Daayana, E. Elkord, U. Winters, et al., Phase II trial of imiquimod and HPV therapeutic vaccination in patients with vulvar intraepithelial neoplasia, *Br. J. Cancer* 102 (7) (2010) 1129–1136, <https://doi.org/10.1038/sj.bjc.6605611>.
- [3] H.W. Buck, K.J. Guth, Treatment of vaginal intraepithelial neoplasia (primarily low grade) with Imiquimod 5% cream, *J Low Genit Tract Dis.* 7 (4) (2003) 290–293.
- [4] C. Grimm, S. Polterauer, C. Natter, et al., Treatment of cervical intraepithelial neoplasia with topical imiquimod: a randomized controlled trial, *Obstet. Gynecol.* 120 (1) (2012) 152–159, <https://doi.org/10.1097/AOG.0b013e31825bc6e8>.
- [5] C.-T. Lin, J.-T. Qiu, C.-J. Wang, et al., Topical imiquimod treatment for human papillomavirus infection in patients with and without cervical/vaginal intraepithelial neoplasia, *Taiwan J Obstet Gynecol.* 51 (4) (2012) 533–538, <https://doi.org/10.1016/j.tjog.2012.09.006>.
- [6] M.M. Koeneman, A.J. Kruse, L.F.S. Kooreman, et al., Preliminary stop of the TOPical Imiquimod treatment of high-grade cervical intraepithelial neoplasia (TOPIC) trial, *BMC Cancer* 17 (1) (2017) <https://doi.org/10.1186/s12885-017-3108-9>.
- [7] C.J. De Witte, A.J.M. Van De Sande, H.J. Van Beekhuizen, M.M. Koeneman, A.J. Kruse, C.G. Gerestein, Imiquimod in cervical, vaginal and vulvar intraepithelial neoplasia: a review, *Gynecol. Oncol.* 139 (2) (2015) 377–384, <https://doi.org/10.1016/j.ygyno.2015.08.018>.
- [8] D.R. Pachman, D.L. Barton, A.C. Clayton, et al., Randomized clinical trial of imiquimod: an adjunct to treating cervical dysplasia, *Am. J. Obstet. Gynecol.* 206 (1) (2012) <https://doi.org/10.1016/j.ajog.2011.06.105>.
- [9] M.P. Schön, Schön M. Imiquimod, Mode of action, *Br. J. Dermatol.* 157 (Suppl. 2) (2007) 8–13, <https://doi.org/10.1111/j.1365-2133.2007.08265.x>.
- [10] L. Nerurkar, A. McColl, G. Graham, J. Cavanagh, The systemic response to topical Aldara treatment is mediated through direct TLR7 stimulation as Imiquimod enters the circulation, *Sci. Rep.* 7 (1) (2017) <https://doi.org/10.1038/s41598-017-16707-5>.
- [11] G. Jin, Z. Lanlan, C. Li, Z. Dan, Pregnancy outcome following loop electrosurgical excision procedure (LEEP) a systematic review and meta-analysis, *Arch. Gynecol. Obstet.* (2014) <https://doi.org/10.1007/s00404-013-2955-0>.