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Treatment of Acne with Isotretinoin Should be Avoided in Patients with Hidradenitis Suppurativa "Conglobata Phenotype"

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Keywords
Hidradenitis suppurativa · Acne vulgaris · Acne conglobata · Isotretinoin · Phenotypes

Abstract
Background: Acne conglobata (AC) and nodulocystic acne have long been confused clinically, despite the presentation and the response to treatment being different. AC and hidradenitis suppurativa (HS) resemble each other; a subtype of HS called "conglobata phenotype" has recently been reported in a large Dutch cohort. Acne vulgaris and HS are often associated. Isotretinoin is typically ineffective in treating HS and may even aggravate it, but it is often indispensable in treating acne vulgaris. ***Objective:*** The aim of the study was to assess whether isotretinoin may be used safely in adults with both HS and acne vulgaris and when it might be contraindicated. ***Materials and methods:*** Belgian HS patients from the European Registry for Hidradenitis Suppurativa Registry (ERHS) reporting a history of severe acne of the face and/or the back, and who have ever used isotretinoin for their acne, were all selected. Patients whose acne worsened on isotretinoin were compared to patients whose acne did not worsen (improvement or no change). ***Results:*** Among the 82 selected patients, 10 (12.2%) report that their acne was aggravated while taking isotretinoin, while 72 (87.8%) report that their acne was not aggravated on isotretinoin. Of the 10 HS patients whose acne worsened with isotretinoin, 9 (90%) were men ($p = 0.04$) and 8 (80%) were HS "conglobata phenotype" ($p < 0.001$). In contrast, 47 (65.3%) of the 72 patients whose acne did not worsen on isotretinoin belonged to the HS "regular phenotype" ($p = 0.01$). On multivariate analysis, the item most strongly associated with poor response to isotretinoin was the HS "conglobata phenotype," followed by body mass index (BMI) (worse response to isotretinoin if BMI >25 kg/m^2). Additionally, of 26 patients who received isotretinoin while their HS had already started, only 6 (23.1%) reported isotretinoin effectiveness on their HS. ***Conclusion:*** Subject to confirmation by larger studies, our study suggests that isotretinoin should be avoided in the treatment of acne in HS patients with the HS "conglobata phenotype," as it may worsen the acne, likewise being male or having a BMI above 25 seems to increase this risk of a bad therapeutic outcome. Patients with an HS "regular phenotype" appear to be at a reduced risk of isotretinoin treatment worsening their acne.

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Introduction

Acne vulgaris (AV), also referred to as just "acne," is a chronic inflammatory dermatosis notable for open or closed comedones and inflammatory lesions, including papules, pustules, or nodules [1]. AV is most commonly affecting the face, less frequently the back and/or chest, and shows a spectrum of signs from mild comedonal acne to aggressive disease, in some cases associated with systemic symptoms (acne fulminans) [2]. AV is among the most common dermatological conditions worldwide [3], and can have a significant negative psychosocial impact, which does not necessarily correlate with the severity of the disease [4].

Acne conglobata (AC) is a rare, highly inflammatory form of acne which presents with grouped comedones, nodules, abscesses, and draining sinus tracts, mainly affecting men and usually starting in adulthood [3, 5], with atypical locations such as the trunk, upper limbs, and buttocks [2]. AC and nodulocystic acne are two forms of severe acne that should not be confused [6]. In 2019, Revuz and Poli [7] established the differences between severe nodulocystic acne and AC according to type of lesions, localizations, and response to treatment. For example, nodulocystic acne does not have sinus tracts and bridges.

Hidradenitis suppurativa (HS), formerly known as acne inversa, is an inflammatory, recurrent skin disease that usually presents after puberty with painful, deep-seated, inflamed lesions mainly in the axillary, inguinal, and anogenital regions [8]. European studies, including undiagnosed patients, estimated that the prevalence can be as high as 1% or even more, thus suggesting that HS is a common condition [9].

Interestingly, there are many similarities between AC and HS [7]: the type of lesions (inflammatory nodules, abscesses, hypertrophic scars, fistulae), certain locations (buttocks, large folds, nape of the neck, retro-auricular region), and above all the response to adalimumab, which is effective in HS [10] and appears promising in treating AC [11]. A distinct subtype of HS called "conglobata phenotype" was first described in 2015 [12] and better illustrated later on in 2021 in a large Dutch cohort [13]. It is defined as a severe type of HS that also includes acneiform lesions (comedones and cysts), extends into ectopic areas such as the face, back, and ears, and occurs more in men than in women. The three other phenotypes of this classification are the "scarring folliculitis phenotype" (icepick scarring, papules, and pustules mainly on the buttocks and pubic region), the "frictional furuncoloid phenotype" (predominantly nodules and abscesses on sites of marked friction), and the "regular phenotype" (default category). It should be noted that there are at least 7 other phenotype classifications, and all are subject to debate [14].

Isotretinoin, an isomer of retinoic acid, is a highly effective treatment for AV [1]. However, isotretinoin represents an ineffective therapeutic option in HS, and may even flare or unmask the disease [15–18]. Other retinoids, such as etretinate or its metabolite, acitretin, are more interesting treatments in HS as they target keratinisation, playing an important role in the terminal hair plugging in HS, rather than the sebaceous gland [19, 20]. According to most treatment guidelines, isotretinoin has no place in the treatment of HS (e.g., European S1 guidelines [20]) or is only indicated in cases of combined HS and AV [21]. More rarely, some guidelines suggest a place for isotretinoin as an alternative to acitretin and in case of failure of other treatments [22], or in preference to acitretin in women of childbearing age [23]. When exceptionally indicated, the aim of treatment with isotretinoin is to treat the acne, rather than the HS, and patients should be made aware of this [24].

The prevalence of AV among adults with HS is significantly higher than among adults without HS [25, 26]. As isotretinoin is effective in treating AV, but may lead to a flare-up of HS, it would be clinically important to know which patient groups could benefit safely from it and when it is potentially contraindicated.

The goals of this investigation were, firstly, to find the determinants of acne response to isotretinoin among HS patients and, secondly, to assess whether isotretinoin could also be an effective treatment for HS. To investigate this, we performed a retrospective study on Belgian patients participating in the European Registry for Hidradenitis Suppurativa (ERHS) project [27, 28].

Materials and Methods

Patients and Design

All Belgian patients from the ERHS project [27, 28] were included in this retrospective study. This registry is a comprehensive questionnaire for patients with HS, including specific questions about AV, isotretinoin use, its efficacy, and a complete physical examination. Therefore, patients were not re-examined or re-contacted by telephone. Among them, patients simultaneously reporting a history of severe acne of the face and/or back and isotretinoin use as acne treatment were selected. Patients who could not remember whether they received isotretinoin were excluded.

As for the efficacy of isotretinoin in treating acne, participants had to select one answer among: "complete efficacy," "partial efficacy," "ineffective without acne aggravation," and "acne

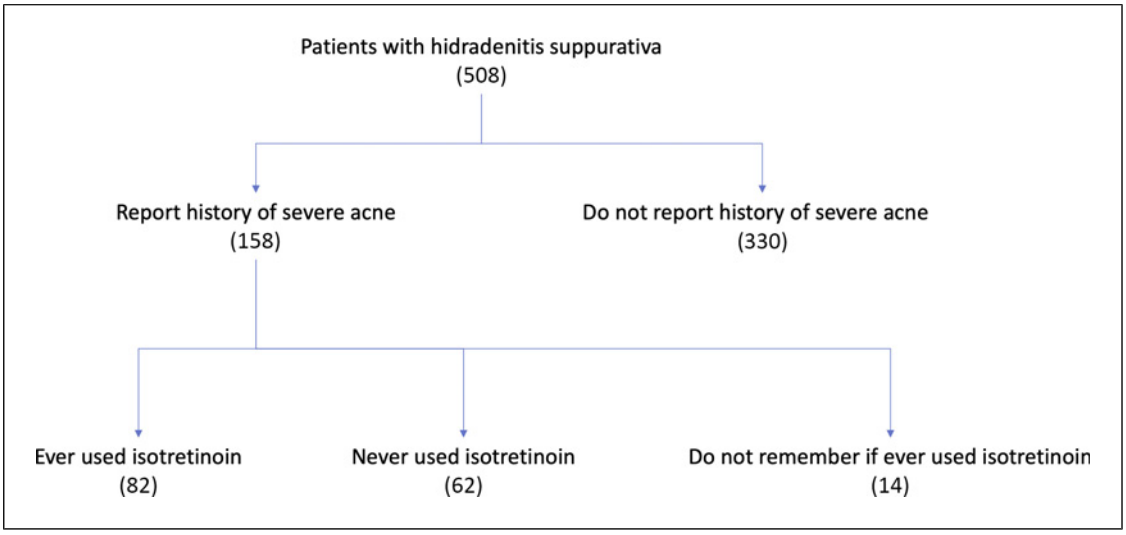

Fig. 1. Efficacy of isotretinoin, among HS patients: patient selection.

aggravation." As for the efficacy of isotretinoin on HS, participants had to select one answer among: "HS aggravated (flared) or precipitated," "HS improved," "HS was not influenced by isotretinoin," or "HS had not started yet."

Statistical Analysis

To limit recall bias and subjectivity, participants were classified into two categories: (1) acne did not worsen under isotretinoin; and (2) acne worsened under isotretinoin. Those two categories were compared according to gender, age at acne onset and end, age at HS onset, body mass index (BMI), medical history, familial history of HS, Hurley score [29], international HS severity score system (IHS4) [30], and van der Zee's phenotypic categories [12, 13].

Statistical analysis was performed using IBM SPSS Statistics 27.0 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as count (percent). Student's *t* test, Fisher exact test, or χ^2 test were used for comparisons between groups, as appropriate. The decision tree, as classification tool, was used to develop a predictive algorithm that identifies the specific factors that differentiate the sample population on the outcome variable that is "efficacy of isotretinoin". All tests were two-tailed and the statistical significance was set at 5% level.

Results

Efficacy of Isotretinoin on Acne

A total of 508 HS patients were included in the Belgian ERHS cohort at the time of analysis. Of these, 158 reported a history of severe acne of the face and/or back, of whom 82 received isotretinoin for their acne (shown in Fig. 1). Of these, 10 (12.2%) reported that their acne worsened with isotretinoin, 23 (28.0%) reported no efficacy of isotretinoin without worsening of acne, 16 (19.5%) reported partial, and 33 (40.2%) reported complete efficacy of isotretinoin on their acne (Table 1).

Secondarily, it should be noted that of the 82 HS patients who received isotretinoin for their acne, 20 had the HS "conglobata type." Of these, only 1 was considered to have both HS and AC (partial efficacy). The remaining 19 had HS with similarities to AC.

In the univariate analysis, of the 10 patients whose acne worsened on isotretinoin, 9 (90.0%) were male ($p = 0.04$) and 8 (80.0%) had the HS "conglobata phenotype" ($p < 0.001$). In contrast, 47 (65.3%) of the 72 patients whose acne did not worsen on isotretinoin belonged to the HS "regular phenotype" ($p = 0.01$) (Table 2). Conversely, age at acne or HS onset, BMI, HS severity scores, family history of HS, and other HS phenotypes did not appear to be associated with acne response to isotretinoin. In multivariable analysis, the HS "conglobata phenotype" followed by BMI >25 were the main determinants of poor acne response to isotretinoin in HS patients (shown in Fig. 2).

Efficacy of Isotretinoin on HS

Among the 82 HS patients that received isotretinoin for their acne, 26 remembered that HS was already present at that time (shown in Fig. 3). Of these, 4 (15.4%) reported an aggravation of HS, 6 (23.1%) reported an improvement of HS, and 15 (57.7%) reported no influence of isotretinoin on HS (Table 3).

Table 1. Effect of isotretinoin on acne among HS patients

Effect of isotretinoin on acne	
Complete efficacy	33 (40.2)
Partial efficacy	16 (19.5)
Inefficient (but non aggravating)	23 (28.0)
Aggravating	10 (12.2)

N (%) presented in each box.

Discussion

Isotretinoin has been shown to be an effective treatment for AV, particularly nodulocystic acne, and is often prescribed in cases of acne associated with HS. However, our results indicate that 12.2% of HS patients have worsening acne on isotretinoin, particularly in the HS "conglobata phenotype," in men, or in cases of overweight or obesity. HS patients with a "regular phenotype" appear to be at a reduced risk of isotretinoin treatment worsening their acne. Secondly, our results confirm the lack of efficacy of isotretinoin as a treatment for HS.

In AV, some patients show a less effective response to isotretinoin than others [31, 32]. However, a transient flare-up of acne with oral isotretinoin occurs in only 6% of cases [33], and cases of acne fulminans are much rarer [34]. The worsening of acne by isotretinoin in our HS patients appears to be therefore at least twice as frequent as in the general population, and moreover is persistent, not transient. Since an inappropriate dose of isotretinoin can lead either to therapeutic ineffectiveness or to a flare-up at the beginning of treatment, it would be interesting to know the dose of isotretinoin received by our patients. In Belgium, in accordance with European guidelines [1], the recommended daily dose of isotretinoin in AV is 0.5 mg/kg (the first month, to minimise the risk of flare-up [35]) to 1 mg/kg, for a cumulative dose of 120–150 mg/kg. Unfortunately, due to the long delay between drug intake and the time of the study, it is obviously impossible to verify that patients have taken this dosage. It should be noted that we did not observe any cases of acne fulminans in our cohort.

As mentioned in the introduction, isotretinoin has no place in the treatment of HS and may even cause flare-ups or unmask latent HS [15–18]. In our cohort, 4 patients described having a worsening of their HS after starting isotretinoin.

The potential mechanisms causing this phenomenon are unclear. Isotretinoin is a potent inhibitor of sebaceous gland activity and is therefore highly effective in AV, in which excessive activation of sebocytes plays a central role [31]. In contrast, in HS, it has been shown that sebum excretion is not excessive [36] and that HS patients even have significantly less sebaceous gland volume than control patients, suggesting that HS may be the consequence of the loss of one or more functions of the sebaceous gland [37]. Indeed, the sebaceous gland is involved in the production of peptides and antibacterial lipids, in hormone synthesis, and in wound healing, but above all, decreased sebocyte activity would facilitate the friction phenomenon and thus cause small epidermal lesions of the sebaceous follicle, leading to release of cellular damage-associated molecular pattern and penetration of microbial components into the skin [38]. The most important result of this study is the association between the HS "conglobata phenotype" and worsening of acne by isotretinoin.

The HS "regular phenotype" was associated with the group whose acne did not worsen on isotretinoin. This obvious difference in response to isotretinoin between these two phenotypes can be readily explained by considering that the acne of the HS "regular phenotype" is AV (caused mainly by hyperseborrhoea) and that the acne of the HS "conglobata phenotype" is actually HS of the face (where sebocytic activity is rather decreased).

This HS "conglobata phenotype" and AC seem to share many similarities, whether in the type of lesions or their location. Our study includes one subject who was actually considered to have both HS and AC, and he was partially responsive to isotretinoin. Even though several cases of AC resistant to isotretinoin but effectively treated with anti-TNF-alpha therapies have been reported, whether the AC is isolated [11] or included in a syndrome, for example, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome [39], it is far from clear that HS and AC are the same disease. Indeed, in these case reports, the patients presented could have HS "conglobata phenotype," not AC. In addition, the doses of isotretinoin received were low in both cases. We therefore consider for the time being that HS conglobata and AC are two diseases that are very similar in many ways but still nosologically distinct.

Nine of the 10 patients with worsening acne were men. This result is in fact a corollary of the HS "conglobata phenotype," which is the only phenotype to include more males than females. It is interesting to note that one of the only major differences between AC and HS is that more women have HS [38], while more men have AC [7].

The role of androgens is well established in the pathophysiology of AV [40] and is possible in AC (association with XYY syndrome, aggravation with hormone

Table 2. Efficacy of isotretinoin, among HS patients: univariate analysis

	Acne did not worsen under isotretinoin (N = 72)	Acne worsened under isotretinoin (N = 10)	p value
Age at acne onset, mean±SD, years	14.2±3.2	13.8±1.8	0.71
Age at acne end, mean±SD, years	22.9±10.7	30.1±10.2	0.09
Age at HS onset, mean±SD, years	18.4±6.4	19.5±6.7	0.64
BMI, mean±SD, kg/m^2	27.1±6.1	27.9±7.5	0.71
IHS4 (mean±SD)	15.4±24.8	24.3±31.1	0.34
Hurley stage, *n* (%)			
1	11 (22.9)	4 (50.0)	
2	33 (68.8)	4 (50.0)	
3	4 (8.3)	0 (0.0)	0.27
Gender, *n* (%)			
Female	34 (47.2)	1 (10.0)	
Male	38 (52.8)	**9 (90.0)**	**0.04**
History of pilonidal sinus, *n* (%)	27 (38.0)	3 (30.0)	0.74
History of PCOS, *n* (%)	3 (9.1)	0 (0.0)	0.99
Family history of HS, *n* (%)	28 (41.2)	3 (33.3)	0.73
HS started during acne period, *n* (%)	50 (69.4)	9 (90.0)	0.27
HS conglobata phenotype, *n* (%)	12 (16.7)	**8 (80.0)**	**<0.001**
HS scarring folliculitis phenotype, *n* (%)	4 (5.6)	0 (0.0)	0.99
HS frictional furuncles phenotype, *n* (%)	9 (12.5)	0 (0.0)	0.59
HS regular phenotype, *n* (%)	**47 (65.3)**	2 (20.0)	**0.01**

Statistical significant findings at 5% level are highlighted in bold. SD, standard deviation; HS, hidradenitis suppurativa; BMI, body mass index; IHS4, international HS severity score system; PCOS, polycystic ovary syndrome.

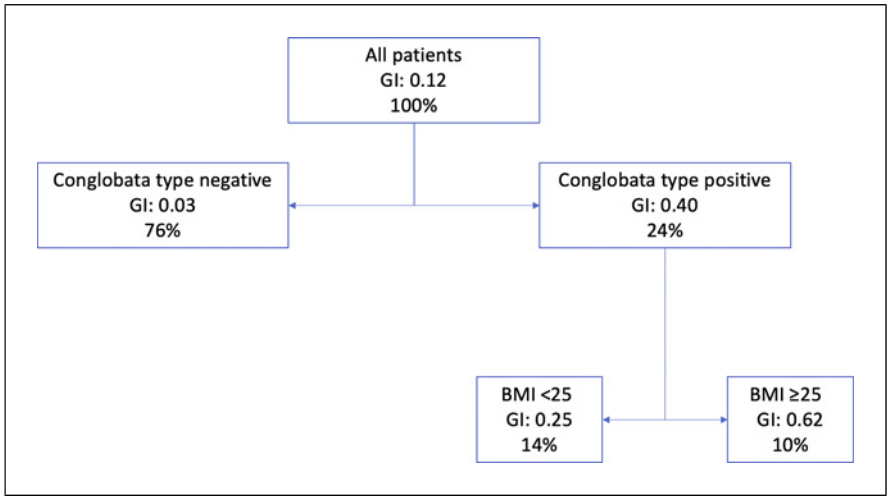

Fig. 2. Efficacy of isotretinoin, among HS patients: classification and regression tree analysis. GI: Gini Impurity of the leaf node.

substitution therapy with testosterone, etc.) [6]. However, in HS, although this role is suggested (female predominance, development of the disease during puberty, premenstrual flare-ups, potential decrease in severity during pregnancy, and menopause), it is still uncertain and requires further clarification [40, 41].

In multivariate analysis, we found an association between worsening acne on isotretinoin and a BMI above 25 in HS patients. Overweight and obesity are well-known risk factors for HS, through increased friction in the large folds, resulting in follicular hyperkeratinization, a wet-occlusive skin-to-skin situation favouring microbial

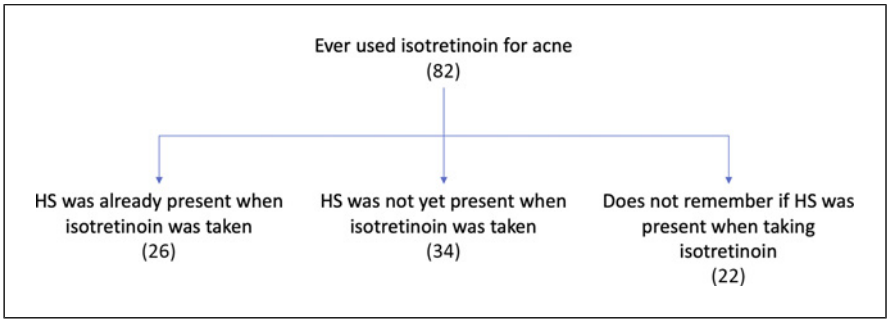

Fig. 3. Efficacy of isotretinoin on HS: patient selection.

Table 3. Effect of isotretinoin on HS

Effect of isotretinoin on HS	
Aggravating (HS flared or revealed)	4 (15.4)
No influence	15 (57.7)
Improvement	6 (23.1)
Does not remember	1 (3.8)

N (%) presented in each box.

overgrowth, and a systemic inflammatory state [42–45]. However, as explained above, the lack of sebocyte activity could accentuate the epidermal damage caused by this friction and isotretinoin would enhance this phenomenon. Additionally, in obese or overweight patients, isotretinoin is sometimes underdosed even if the treatment is of longer duration [46].

The presence of a pilonidal sinus is sometimes presented as a factor predicting a good response to isotretinoin in HS [47]. We found it interesting to observe whether the presence of a pilonidal sinus would be a factor predicting a good response to isotretinoin in acne among HS patients, but this is not the case despite 30 patients (36.6%) reporting a history of pilonidal sinus.

The main limitation of this study is its retrospective nature, and therefore the presence of a potential recall bias, which prevents us from precisely knowing the dose of isotretinoin received. The efficacy of isotretinoin on the patient's acne is assessed here solely based on a subjective question, with no objective score.

Conclusion

Treatment of patients with both AV and HS can be a challenge: isotretinoin has a prominent place in the treatment of AV, especially in nodulocystic acne, but can cause flares in HS. Subject to confirmation by larger and ideally prospective studies, our study suggests that isotretinoin should be avoided in the treatment of acne in HS patients with the HS "conglobata phenotype," as it may worsen the acne, likewise being male or having a BMI above 25 seems to increase this risk of a bad therapeutic outcome. Patients with an HS "regular phenotype" appear to be at a reduced risk of isotretinoin treatment worsening their acne.

Key Message

Acne could worsen under isotretinoin in patients with hidradenitis suppurativa "conglobata phenotype."

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Statement of Ethics

All the data used in this study came from the European Registry for Hidradenitis Suppurativa (ERHS), whose project was approved by the Ethics Committee of *Hôpital Erasme* (Erasme Ethical Committee P2015/071). All subjects have given their written informed consent.

Conflict of Interest Statement

Mathieu Daoud, Mariano Suppa, Stéphanie Heudens, Mathilde Daxhelet, Hassane Njimi, Laura Nobile, Julio Tannous, Claire Van Damme, Jalila Karama, Jonathan M White, Jean Revuz, Farida Benhadou, and Véronique del Marmol have no conflicts of interest to declare.

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Author Contributions

Mathieu Daoud, Mariano Suppa, Mathilde Daxhelet, Hassane Njimi, Farida Benhadou, and Véronique del Marmol conceptualized the project and participated in its methodology. The formal analysis was done by Mathieu Daoud and Hassane Njimi. Mathieu Daoud, Mariano Suppa, Stéphanie Heudens, Mathilde Daxhelet, Laura Nobile, Julio Tannous, Claire Van Damme, Jalila Karama, and Farida Benhadou actively participated in the data collection. Mathieu Daoud, Stéphanie Heudens, Hassane Njimi, Laura Nobile, Julio Tannous, Claire Van Damme, Jalila Karama were responsible for data curation. The original draft has been written by Mathieu Daoud, and conscientiously reviewed by Mariano Suppa, Stéphanie Heudens, Mathilde Daxhelet, Hassane Njimi, Laura Nobile, Julio Tannous, Claire Van Damme, Jonathan White, Jean Revuz, Farida Benhadou, and Véronique del Marmol for the content and for the form. The visualization of the data was done by Mathieu Daoud, Hassane Njimi, and Mariano Suppa. Supervision was provided by Véronique del Marmol.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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