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**Isotretinoin treatment in severe peanut- and soy-allergic patients: is it safe or not?**  
 --Manuscript Draft--

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1 **Submission to JIACI: Practitioner's Corner**

2 **Isotretinoin treatment in severe peanut- and soy-allergic**  
3 **patients: is it safe or not?**

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23 This data have been presented at a National Meeting of the Belgian Society of Allergy and Clinical  
24 Immunology on November 25<sup>th</sup>, 2017.

25

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32 MM: none

33 CB: CB is recipient of a Clinical Research Fund of the University Hospitals Leuven.

34

35 Conflicts of interest:

36 No conflicts of interest to disclose with regard to this short clinical communication.

37

38 Key words: Peanut, soy, soybean oil, isotretinoin, allergy

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40 Patient's consent and permission to publish

41 The patient described in this case report, did consent to publication.

42

## 1 **Practitioner's corner**

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### 3 **Isotretinoin treatment in severe peanut- and soy-allergic patients: is it safe or not?**

4 Isotretinoin is contra-indicated in patients with peanut and/or soy allergy. We present a case of a  
5 successful oral provocation of isotretinoin in a patient with both primary peanut and soy allergy, and  
6 suggest a stepwise work-up of these patients.

7 A 25-year old male, suffering from severe acne and a history of allergic asthma, rhinoconjunctivitis and  
8 reported allergic reactions to peanut in childhood, was referred to the Allergy department by his  
9 dermatologist to evaluate the safety of isotretinoin. The prescribing information leaflet states that  
10 isotretinoin is contraindicated in patients with known soybean or peanut allergy, owing the risk of  
11 potential cross-reactivity. All oral isotretinoin formulations (in Belgium) contain soybean oil. However,  
12 data about the safety of isotretinoin in patients with potential severe peanut and/or soybean allergy  
13 are scarce<sup>1-4</sup>.

14 The patient avoided peanuts and soybean products since childhood, because of several allergic  
15 reaction in childhood with facial swelling, itching and dyspnoea immediately after eating peanuts or  
16 food containing peanut or arachide oil. He never experienced reactions due to soy, although careful  
17 dietary history suggested absence of exposure to soy-containing food. An allergy workup was  
18 performed. Skin prick tests (SPT) were positive for peanut extract (4+) and soy milk (4+). Specific IgE  
19 (sIgE, ImmunoCAP Thermofisher/Phadia, Uppsala, Sweden) to the crude extract of peanut and the  
20 stable 2S-albumin seed storage protein of peanut Ara h 2, associated with systemic reactions to  
21 peanut<sup>5</sup>, were both > 100 kU/L. Also sIgE for the other seed storage proteins of peanut (Ara h 1 and  
22 Ara h 3) was detected (respectively > 100 kU/L and 36.30 kU/L) without relevant Bet v 1 or LTP  
23 sensitisation (Ara h 8 and ara h 9 respectively 0.12 kU/L and 0.16 kU/L). sIgE for the crude extract of  
24 soy, the stable seed storage proteins of soy, Gly m 5 and Gly m 6, associated with severe allergic

25 reactions<sup>6</sup>, and the Bet v 1-crossreactive allergen Gly m 4, were respectively 6.82 kU/L, 12.70 kU/L and  
26 < 0.10 kU/L (normal <0.10 kU/L); total IgE 915 kU/L. SPT with the capsule and content of 3 isotretinoin  
27 containing products available in Belgium (Isosupra<sup>®</sup>, Isotretinoine EG<sup>®</sup> and Roaccutane<sup>®</sup>), all  
28 containing soybean oil, were negative. A subsequent open oral challenge with Isotretinoine EG<sup>®</sup> (0.01–  
29 0.1–1–10–20–100%, cumulative dose 131.11%, 13.11 mg) was negative. Due to the oil content within  
30 the capsule, we dissolved the Isotretinoine in hot milk, in order to be able to perform an updosing  
31 protocol. After this successful provocation, long term treatment with isotretinoin was successfully  
32 initiated.

33 Peanut and soy are phylogenetically and antigenetically related to each other and share several  
34 homologous proteins. Patients with severe peanut allergy are at risk to develop also severe reactions  
35 to soy<sup>7</sup>. Soybean oil still contains soy proteins and therefore, isotretinoin, containing soybean oil, is  
36 contraindicated in patients with known soybean or peanut allergy, owing the risk of potential cross-  
37 reactivity. However, it has been demonstrated earlier that the allergenicity of proteins in soybean oil  
38 is very little with regard to soybean allergy<sup>8</sup>. In literature, only one case is reported of potential  
39 anaphylaxis after a first dose of isotretinoin in a patient with a minor sensitisation to soybean (Gly m 4  
40 1.38 kUA/L)<sup>9</sup>. However, it remains arguable whether isotretinoin was the culprit of the reaction: the  
41 27-year-old patient, with known cashew nut allergy, developed only 12 hours after the first dose of  
42 isotretinoin facial swelling and was able to continue the treatment for 3 days. They report the  
43 successful initiation of treatment with isotretinoin in 4 patients with negative SPT and sIgE for soybean.  
44 Only 3 cases of successful oral provocation with isotretinoin in peanut allergic patients are reported.  
45 Only in one case, a low sIgE for soybean (0.39 kU/L) was detected, however this patient did not report  
46 any allergic reactions to soy and was not avoiding soy in his diet (**Table 1**)<sup>1-3</sup>. Spierings et al. describe a  
47 successful introduction of isotretinoin in 6 patients with known severe peanut allergy, however the  
48 results of component-specific IgE are not reported<sup>4</sup>. These patients were challenged uneventfully in  
49 the hospital.

50 We present here an oral provocation strategy for isotretinoin with increasing dosage, feasible in high  
51 risk patients with both severe soybean- and/or peanut allergy. The prescribing leaflet states that oral  
52 isotretinoin is contraindicated in patients with known soybean or peanut allergy. Therefore, we  
53 suggest, as stated by others, that there is probably only a theoretical risk for allergic reactions to  
54 isotretinoin, even in patients with a severe primary peanut and/or soybean allergy<sup>10</sup>.

55 Based on our results and previous case reports, we suggest the following steps before initiation of  
56 isotretinoin in patients with potential soybean and/or peanut allergy:

- 57 1. Establish a correct diagnosis of soybean- and/or peanut allergy based on history, SPT and sIgE  
58 (at least Ara h 2, Gly m 5, Gly m 6) determination.
- 59 2. In case of Bet v 1-associated soybean- and/or peanut allergy, isotretinoin can be started safely  
60 at home without any precautions.
- 61 3. In case of (severe) primary soybean- and/or peanut allergy, depending on the risk estimation  
62 and necessity of the regimen, a first intake under medical supervision can be performed with  
63 a follow-up for 1 hour. In high risk patients or in children, an oral provocation with isotretinoin  
64 solved in hot milk can be performed in a hospital setting as described in our case.

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## 66 **References**

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92 **Table 1:** Summary of the reported cases in literature of oral provocation of isotretinoin in patients with  
93 soybean and/or peanut allergy. Abbreviations: SPT: skin prick test, NR: not reported.

94

	Case 1 <sup>1</sup>	Case 2 <sup>2</sup>	Case 3 <sup>3</sup>	Our case
<b><i>Skin prick testing</i></b>				
SPT peanut	positive	positive	positive	positive
SPT soy	negative	NR	positive	positive
SPT Isotretinoin	negative	negative	negative	negative
<b><i>Specific IgE (immunoCAP)</i></b>				
Total IgE (kU/L)	959	817	4229	915
Peanut (kU/L)	3,93	NR	35,7	> 100
Ara h 2 (kU/L)	0,72	4,12	7,97	> 100
Ara h 8 (kU/L)	NR	9,74	3,72	0,12
Ara h 9 (kU/L)	NR	NR	NR	0.16
Soy (kU/L)	<0,35	NR	0,39	10,20
Gly m 5 (kU/L)	NR	NR	NR	6,82
Gly m 6 (kU/L)	NR	NR	NR	12,70
<b><i>Oral provocation</i></b>				
Isotretinoin	negative	negative	negative	negative

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## 1 Practitioner's corner

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12 However, data about the safety of isotretinoin in patients with potential ~~primary-severe~~ peanut and/or  
13 soybean allergy are scarce<sup>1-4</sup>.

14 The patient avoided peanuts and soybean products since childhood, because of several allergic  
15 reaction in childhood with facial swelling, itching and dyspnoea immediately after eating peanuts or  
16 food containing peanut or arachide oil. without any investigation before. He mentioned several allergic  
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Ara h <sub>8</sub> (kU/L)	NR	9,74	3,72	0,12
<b>Ara h<sub>9</sub> (kU/L)</b>	NR	NR	NR	0.16
Soy (kU/L)	<0,35	NR	0,39	10,20
Gly m <sub>5</sub> (kU/L)	NR	NR	NR	6,82
Gly m <sub>6</sub> (kU/L)	NR	NR	NR	12,70
<b>Oral provocation</b>				
Isotretinoin	negative	negative	negative	negative

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**Ref.: Ms. No. JIACI-D-18-00210R1**

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**EDITOR'S SPECIFIC COMMENTS:**

**Cross referencing: we would like to emphasise that we attach great importance to cross referencing very recent material on the same topic published in „J Investig Allergol Clin Immunol". Therefore, it would be highly appreciated if you would check the last two years ([www.jiaci.org](http://www.jiaci.org)) and add all material relevant to your article to the reference list.**

We checked the material published in „J Investig Allergol Clin Immunol" but did not find any material related to this topic.

**REVIEWERS' COMMENTS:**

**Line 5: Remove primary.**

We removed 'primary' in the text.

*We present a case of a successful oral provocation of isotretinoin in a patient with both ~~severe~~ primary peanut and soy allergy, and suggest a stepwise work-up of these patients.*

**Line 8: Add "allergic reaction..."**

We added 'allergic' in the text.

*A 25-year old male, suffering from severe acne and a history of allergic asthma, rhinoconjunctivitis and reported allergic reactions to peanut in childhood, was referred to the Allergy department by his dermatologist to evaluate the safety of isotretinoin.*

**Line 11: - remove "marketed" : All oral isotretinoin formulations marketed (in Belgium) contain soybean oil.**

We removed 'marketed' in the text.

*All oral isotretinoin formulations ~~marketed~~(in Belgium) contain soybean oil.*

**Line 12: Remove primary.**

We removed 'primary' in the text and corrected a typing error.

*However, data about the safety of isotretinoin in patients with potential ~~primary~~ severe peanut and/or soybean allergy are scarce<sup>1-4</sup>.*

**Line 14 - 18: Rephrase this idea for clarity**

We rephrased this paragraph based on these comments. The text sounds now:

*The patient avoided peanuts and soybean products since childhood, because of several allergic reaction in childhood with facial swelling, itching and dyspnoea immediately after eating peanuts or food containing peanut or arachide oil. ~~without any investigation before. He mentioned several allergic reaction in childhood with facial swelling, itching and dyspnoea immediately after eating peanuts or food containing peanut or arachide oil.~~*

**Line 35: containing soybean oil, is...**

We changed 'was' to 'is' in the text.

*Soybean oil still contains soy proteins and therefore, isotretinoin, containing soybean oil, ~~was~~ is contraindicated in patients with known soybean or peanut allergy, owing the risk of potential cross-reactivity.*

**Line 51: Remove primary**

We removed primary in the text.

*We present here an oral provocation strategy for isotretinoin with increasing dosage, feasible in high risk patients with both severe ~~primary~~ soybean- and/or peanut allergy.*

**Editor's comments:**

**In the final editing, please use the correct international nomenclature for allergens, i.e. put a space between the letter of the species and the number**

We corrected this throughout the text and changed the name to the correct nomenclature.