Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Consequences of Discontinuing a 4/6 Cyclin D-Dependent Kinase Inhibitor During Endocrine Treatment in Hormone-Sensitive Metastatic Breast Cancer Patients in the Context of the COVID-19 Outbreak

Sophie Martin,1 Carole Pflumio,1 Philippe Trensz,1 Frederique Schaff-Wendling,2 Michal Kalish-Weindling,1 Cathie Fischbach,1 Laure Pierard,1 Jean-Marc Limacher,3 Rita Nader,1 Michel Velten,4,5 Thierry Petit1

Abstract

The impact of some oncology interventions taken hastily during the COVID-19 first wave remains unknown. This non-interventional, retrospective, multicentric study was conducted to assess the consequences of CDK 4/6i interruption in patients with metastatic breast cancer. Results showed disease progression in 37% of patients, and the risk of metastatic disease progression was significantly increased for patients with liver metastases.

Background: The impact of some hasty medical decision made during the first wave of the Coronavirus Disease 2019 (COVID-19) remains unknown. We have evaluated the consequences of one of these precautionary measures: the withdrawal of the cyclin D-dependent kinases 4/6 inhibitor (CDK4/6i) in patients whose metastatic disease was controlled by a combination of endocrine treatment and CDK 4/6i. Method: This study was noninterventional, retrospective, multicentric, and included 60 patients with HR+ HER2- metastatic disease. Their disease was controlled with the combination of endocrine treatment and CDK 4/6i. The CDK 4/6i was stopped for two months during the first COVID-19 outbreak. A univariate analysis was performed to assess the risk factors associated with disease progression. Results: During this therapeutic break, 22 (37 %) patients had a radiological and/or clinical disease progression. Among them, the CDK 4/6i was re-introduced to 16 patients (n = 16/22; 73 %). A new line of treatment (chemotherapy or targeted therapy) was initiated due to the rapid symptomatic tumor progression in four patients (n = 4/22; 18 %). Two patients (n = 2/22) died in visceral crisis before another anti-tumoral treatment was introduced. In univariate analysis, the presence of liver metastases increased the risk of metastatic disease progression during the withdrawal of the CDK 4/6i (OR = 6.6; 95 % CI 1.87-23.22; P= .0033). Conclusion: Progression was observed in 37% of patients during the two-month treatment interruption of the CDK 4/6i. A prolonged CDK 4/6i treatment interruption in patients with clinical benefit on endocrine treatment does not seem to be a reasonable option in light of these results.

Clinical Breast Cancer, Vol. 23, No. 1, 32–37 © 2022 Elsevier Inc. All rights reserved.

KEYWORDS: COVID-19, Disease progression, Hepatic metastases, Treatment withdrawn, CDK4/6 inhibitors

---

Abbreviations: CDK4/6i, cyclin D-dependent kinases 4/6 inhibitors; CI, confidence intervals; COVID-19, Coronavirus Disease 2019; HER-2, human epidermal growth factor receptor-2; HR, hormone receptor; ICANS, Institut de Cancérologie Strasbourg, Europe; LHRH, luteinizing hormone-releasing hormone; OR, Odds Ratio; OS, overall survival; p, P value; RR, Relative risk; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SBR, Scarff Bloom Richardson.

1Department of Medical Oncology, Strasbourg Cancer Institute (ICANS), Strasbourg, France
2Department of Medical Oncology, Clinique de l’Orangerie, Strasbourg, France
3Department of Medical Oncology and Clinical Hematology, Hôpital Louis Pasteur, Colmar, France
4Department of Epidemiology and Public Health, Strasbourg University, Inserm, Strasbourg, France
5Department of Public Health, ICANS, Strasbourg, France

Submitted: Mar 21, 2022; Revised: Sep 27, 2022; Accepted: Oct 9, 2022; Epub: 13 October 2022

Address for correspondence: Sophie Martin, Department of Medical Oncology, ICANS, 17 rue Albert Calmette, BP 23025, 67033, Strasbourg, France.

E-mail contact: s.martin@icans.eu
Introduction

As it has been more than a year since the emergence of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) responsible for the current COVID-19 pandemic, it is worthwhile to evaluate the medical methods that were taken in emergency during the first wave of the epidemic. The region of Eastern France classified in this time as one of the first national clusters, had to face an unprecedented health crisis and a massive influx of infected persons, including patients with solid tumors. These patients were considered fragile and vulnerable both due to their malignant pathology and anti-cancer therapies, which can cause a deep and lasting state of immunosuppression.

Therefore, precautionary and preventive measures to reduce severe risks and potentially fatal infections have been recommended in oncology practice before the publication of more precise guidelines by various scientific societies. The French guidelines, published in May 2020, discussed the management of patients with hormone receptor (HR)-positive and human epidermal growth factor receptor-2 (HER-2)- negative metastatic breast cancer treated with hormone therapy in combination with a selective cyclin-D dependent kinases 4/6 inhibitor (CDK 4/6i). It was recommended to stop the CDK 4/6i in patients whose disease was controlled by the combination of this targeted therapy with endocrine treatment. The main argument for this recommendation was to reduce the risk of myelosuppression (in particular neutropenia, a predictive factor of unfavorable evolution of COVID-19), and symptoms (such as diarrhea, asthenia, or cardiac rhythm disorders), that may have overlapped with similar symptoms described in SARS-CoV-2 infections.

In accordance with these guidelines, after a case-by-case assessment showing a benefit outweighing the risks of such an approach, the CDK 4/5i was stopped in patients with a complete or partial response or clinical benefit with the combination of endocrine treatment and CDK 4/6i.

After several months of follow-up, we present the impact of stopping a CDK 4/6i among this patient population.

Patients and Methods

Study design

This is a multicentric, retrospective study conducted in three Alsatian centers including ICANS (Institut de Cancérologie Strasbourg-Europe), Clinique de l’Orangerie (ELSAN Group, Strasbourg) and Hôpital Civil Louis Pasteur (Colmar).

All included patients had an HR+ HER2- metastatic breast cancer treated with a combination of endocrine treatment (Fulvestrant or aromatase inhibitor) and CDK 4/6i. Their disease had to be clinically, radiologically, and biologically controlled before inclusion. The CDK 4/6i treatment was interrupted, during the first COVID-19 outbreak, in accordance with the French guidelines for clinical practice.

Disease progression during the CDK 4/6i discontinuation was assessed clinically (eg, increase of a palpable mass, the appearance of subcutaneous nodules, or worsening of symptoms) or radiologically (CT, bone scan, or TEP-scan). Following current recommendations, a single elevation of the tumor marker CA 15.3 was insufficient to confirm disease progression.

The tumors were identified as luminal B if two of the following three criteria were identified: Scarff Bloom Richardson (SBR) histologic grade = 3, Ki 67 proliferation index ≥20%, Progesterone receptor expression ≤20%. The other tumors were classified as luminal A. Diseases were classified into 3 groups according to their sensitivity to endocrine treatment before CDK 4/6i prescription: endocrine treatment naïve, primary resistance defined as any disease progression during the first two years of adjuvant hormonal therapy or during the first 6 months in the metastatic setting, and secondary resistance for all other situations.

Study objectives and statistical analysis

The main objective was to evaluate the consequences of prolonged discontinuation of CDK 4/6i in patients whose disease was controlled by the combination of endocrine treatment and CDK 4/6i.

The following parameters were investigated for their prognostic role on disease progression: Tumor type (Luminal A vs. Luminal B), endocrine sensitivity, endocrine treatment (aromatase inhibitor vs. Fulvestrant), metastatic site, duration of CDK 4/6i treatment before withdrawal, and duration of the CDK 4/6i withdrawal.

All records were blinded before statistical analysis. Response analysis was performed by univariate logistic regression. As only one effect was significant in the univariate analysis, we did not perform a multivariate analysis since it was unlikely that there were other significant effects given the size of the population analyzed.

Results

Patient characteristics

Between January 5th and March 11th 2021, 60 patients were included (35 patients at ICANS, 18 patients at the Colmar hospital, and 7 patients at the Orangerie Clinic). Patients and their disease characteristics are presented in Table 1. The median age of the patients was 65 years (35-93 years). The majority of patients were in good general condition (ECOG performance status of 0 or 1 for 50 patients, 2 for 10 patients).

One-third of the patients were on second-line endocrine therapy (n = 20, 33 %) and 34 (57 %) were classified as having secondary hormonal resistance. Based on pathological criteria of the primary tumor or a secondary lesion, 47 patients (78 %) had a Luminal A tumor while 13 patients (22%) had a Luminal B tumor.

CDK 4/6 inhibitors and the first epidemic wave of COVID-19

The CDK 4/6i included Palbociclib in 49 patients (82%), Ribociclib in eight patients (13%), and Abemaciclib in 3 patients (5 %). The CDK 4/6i was given in combination with Fulvestrant in 35 patients (58 %), or with an AI in 25 patients (42%) patients. Ovarian suppression with luteinizing hormone-releasing hormone (LHRH) analogs was also prescribed in eight patients. The median duration of CDK 4/6i treatment before the withdrawal was 10.3 months. The CDK 4/6i treatment was initiated for 6 months in 25 patients (42 %), one year in 17 patients (28 %), and more than one year in 18 patients (30 %).

The average duration of the CDK 4/6i withdrawal was 8 weeks (4-19 weeks).
Thirty-eight patients (38/60 = 63%) had no clinical or radiological evidence of disease progression at the time of the CDK 4/6i reintroduction (Figure 1). In four of those patients, the CA 15,3 tumor marker had increased significantly but without any new clinical symptoms or radiological progression. One year later, in January 2021, thirty-five patients (35/38 = 92%) were still on the combination of endocrine treatment and CDK 4/6i.

Tumor progression was observed in 22 patients (22/60 = 37%) during the CDK 4/6i interruption period, with 15 patients with a radiological progression and 7 patients with a clinical progression. Among these 22 patients, CDK 4/6i was reintroduced in 16 patients (16/22 = 73%), assuming that the targeted therapy reintroduction would lead to either stabilization of the disease or therapeutic response. A new therapeutic response (partial response or tumor stabilization) was observed in 7 patients (7/16 = 43%).

A new treatment (chemotherapy or PARP inhibitor) was initiated in 4 patients (4/22 = 18%), because of major tumor progression. Two patients (2/22 = 9%) had a major progression with visceral crisis and died before the possibility of reintroducing a new anti-tumoral treatment.

**Prognostic factors associated with disease progression**

All the results of the univariate analysis are summarized in the Table 2. The presence of liver metastases was the only prognostic factor in univariate statistical analysis. The risk of disease progression after CDK 4/6i discontinuation was increased 5.5-fold if patients had liver metastasis.

The risk of tumor progression was similar, after CDK 4/6i discontinuation, with aromatase inhibitor (9/25 = 36%) or Fulvestrant (13/35 = 37%; P = .92).

Although not statistically significant (P = .15), the risk of progression for the luminal B subtype appeared to be 2.49 times higher than for the luminal A subtype. This risk was also increased (2.38-fold) when the CDK 4/6i was stopped more than two cycles, compared to a shorter period.

**Discussion**

The CDK 4/6i has revolutionized the management of patients with hormone-sensitive metastatic breast cancer. PALOMA-2 and 3 were the first randomized phase III trials comparing HT alone vs. HT plus a CDK 4/6i and demonstrated a disease progression-free survival (PFS) benefit in this patient population.9,20

The benefit was seen both in the first-line setting, with a PFS of 24.8 months vs. 14.5 months (Palbociclib + Letrozole vs. Letrozole alone; HR = 0.58; 95% CI 0.46-0.72; P < .000001), and in the second-line setting, with a PFS of 9.2 months vs. 5.8 months (Palbociclib + Fulvestrant vs. Fulvestrant alone; HR = 0.48; 95% CI 0.27 to 0.86; P = .0065) in patients previously treated with non-steroidal AI therapy.
Table 2  Univariate Analysis and Odds Ratio for Disease Progression

| Tumor subtype                        | OR  | 95% CI      | P Value |
|--------------------------------------|-----|-------------|---------|
| Luminal A                            | 1   |             | .15     |
| Luminal B                            | 2.49| [0.71-8.70] |         |
| **Hormone sensitivity**              |     |             |         |
| Hormone sensitive                    | 1   |             | .07     |
| Primary or Secondary hormone resistance | 3.27| [0.93-11.54] |         |
| **Metastatic sites**                 |     |             |         |
| Exclusive bones metastases          | 1   |             | .01     |
| Liver metastases (not exclusive)     | 5.50| [1.14-26.41] |         |
| Visceral metastases (not hepatic)    | 0.76| [0.18-3.20] |         |
| **Duration of CDK 4/6i treatment before withdrawn** |     |             |         |
| <6 months                            | 1   |             | .70     |
| Between 6 months and 12 months       | 1.16| [0.31-4.26] |         |
| >12 months                           | 1.70| [0.49-5.95] |         |
| **Duration of CDK 4/6i treatment withdrawn** |     |             |         |
| <2 months                            | 1   |             | .12     |
| ≥2 months                            | 2.38| [0.79-7.15] |         |

Abbreviations: CI = confidence interval; OR = odds ratio; vs = versus; CDK 4/6i = 4/6 cyclin D-dependent kinase inhibitor.

With a longer follow-up, numerous studies have demonstrated a significant improvement in overall survival in first line-setting (Monaleesa 2, 3, and 7 with Ribociclib) and second-line (Monarch 2 with Abemaciclib and Paloma 3 with Palbociclib).19,21

At the time of the first COVID-19 epidemic peak, temporarily stopping these targeted therapies seemed reasonable given their respective adverse effects, which were assumed to be risk factors for a more severe COVID-19 infection.11

Furthermore, reassuring data were extracted from these randomized studies showing that CDK 4/6i dose-reduction for toxicity did not reduce the benefit of CDK 4/6i addition to endocrine treatment.22,23

The present study is the first to evaluate the withdrawal of the CDK 4/6i in patients whose disease was controlled by the combination of endocrine treatment and CDK 4/6i. There was disease progression in more than one-third of the patients with CDK 4/6i withdrawn. This observation demonstrates that it is not reasonable to stop CDK 4/6i and continue only the endocrine treatment, even in women with disease stability. These data are useful in clinical practice, providing some answers to patients with a long-lasting...
Consequences of Discontinuing a 4/6 Cyclin D-Dependent Kinase

efficacy of the combination of endocrine treatment with CDK 4/6i who would like to lighten their treatment. On the contrary, it was demonstrated that CDK 4/6i dose reduction was possible, with a maintained benefit of the combination of endocrine treatment with CDK 4/6i.24,25

The CDK4/6i are interrupted in various situations. Toxicity may require dose interruptions. Stopping the CDK4/6i treatment is a common practice in perioperative period or during radiation therapy. However, these interruptions are usually short.26,27

As shown in our study, interruptions of more than 4 weeks might put the patients at risk of progression. Therefore, physicians must carefully consider this risk before interrupting the CDK4/6i for long periods of time, more specifically for patients with liver metastasis.

This study shows that liver metastasis significantly increased the risk of tumor progression during the CDK 4/6i withdrawal (OR = 5.50; CI 1.14-26.4; P = .01).

This study has some limitations since it is retrospective, limited to three centers and a small number of patients. Nonetheless, radiological assessment was performed before the withdrawal of CDK 4/6i and before their resumption, and tumor progression was defined according to RECIST 1.1 criteria.

Lastly, this management was placed in a context of an unprecedented health crisis, having to face a viral pandemic from an unknown infectious agent resulting in hasty and uncodified therapeutic decisions.14

Conclusion

The COVID-19 pandemic led to health care system restructuring and current practice adjustments following our understanding of SARS-CoV-2 over time. Thus, our study highlights the consequences of certain therapeutic decisions, decided in an emergency and without a strong scientific basis. Prolonged CDK 4/6i discontinuation in patients with controlled metastatic cancer is not a reasonable option, as there was disease progression in more than one third of patients during this interruption.

Clinical Practice Points

• Discontinuation, even temporarily, of CDK 4/6i cyclin D kinases inhibitors resulted in disease progression in more than one-third of patients whose disease was controlled by the combination of endocrine treatment and CDK 4/6i.

• The risk of metastatic disease progression was significantly increased for patients with liver metastases.

• Discontinuation or even temporary interruption of the CDK 4/6i in patients with controlled metastatic disease is highly discouraged.

Authors contribution

Sophie Martin performed conceptualization, methodology, investigation, formal analysis, and Writing - Original Draft. Carole Pflumio, Philippe Trens, Frederique Schaff-Wendling, Michal Kalish-Wendling, Cathie Fischbach, Laure Pierard, Jean Marc Limacher, Rita Nader, and Michel Velten performed resources, investigation, and Writing - Review & Editing. Michel Velten performed formal analysis and Writing - Review & Editing. Thierry Petit performed Writing- Review & Editing, Validation, Visualization, Supervision, and Project administration.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

T.P. reports grants from Pfizer, Novartis, AstraZeneca, Lilly, and Pierre Fabre, but which were unrelated to the submitted work. Other authors declare no conflicts of interest related to this manuscript.

References

1. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) in China. 2020. http://www.chinacdc.cn/en/article/id/e5946e2-c6ec-41e9-9b9b-fea8d18af51. Accessed 7 Nov 2020.

2. Shankar A, Saini D, Roy S, et al. Cancer care delivery challenges amidst Coronavirus Disease –19 (COVID-19) outbreak: specific precautions for cancer patients and cancer care providers to prevent spread. Asian Pacific J Cancer Present. 2020;20(1):569–573. doi:10.31557/APJCP.2020.21.3.569.

3. Hanna TP, Evans GA, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. Nat Rev Clin Oncol. 2020;17(5):1–3. doi:10.1038/s41571-020-0362-y.

4. Martin S, Kaeuffer C, Leyendecker P, et al. COVID-19 in patients with cancer: a retrospective study of 212 cases from a French SARS-CoV-2 cluster during the first wave of the COVID-19 pandemic. Oncology. 2021;80:e1656–1659. 2021 Sep. doi:10.1159/00034831.

5. . Agence Régionale de Santé Grand Est. 2020. https://www.gran-est.sante.fr/

6. Musseit A, Malaquifer C, Albazaun-Puig A, et al. Handling the COVID-19 pandemic in the oncological setting. Lancer Haematol. 2020. doi:10.1016/S2652-3026(20)30108-3.

7. Cortiella F, Petret A, Bartolotti M, et al. Managing COVID-19 in the oncology clinic and avoiding the distraction effect. Ann Oncol. 2020. doi:10.1016/j.annonc.2020.03.286.

8. de Azambuja E, Trapani D, Loibl S, et al. ESMO Management and treatment adapted recommendations in the COVID-19 era. Breast Cancer. ESMO Open. 2020;5. doi:10.1136/esmoopen-2020-000793. SUPPLEMENT 3, E000793.

9. You B, Ravaud A, Canivet A, et al. The official French guidelines to protect patients with cancer against SARS-CoV-2 infection. Lancer Oncol. 2020;21(5):619–621. doi:10.1016/S1470-2045(20)30240-7.

10. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancer. 2020.

11. Gligorov J, Bachelor T, Pierga J-Y, et al. COVID-19 and personnel suivies for a cancer du sein: recommandations françaises pour la pratique clinique de Nice-St Paul de Vence, in collaboration with the Collège National des Gynécologues et Obstétriciens français (CNGOF), la Société d’Imagerie de la Femme (SIFEM), la Société Française de Chirurgie Oncologique (SFCO), la Société Française de Sémiologie et Pathologie Mammare (SFSPM) et le French Breast Cancer Intergroup-UNICANCER (UCBG). Bull du Cancer. 2020;107:528–537. doi:10.1016/bulcan.2020.03.008.

12. Rossi V, Berchialla P, Giannarelli D, et al. Should all patients with HR-positive HER2- negative metastatic breast cancer receive CDK 4/6 inhibitor as first-line based therapy? A network meta-analysis of data from the PALOMA 2, MONALEESA 2, MONALEESA 7, MONARCH 3, FALCON, SWOG, and FACT Trials. Cancers (Basel). 2019;11:1661. doi:10.3390/cancers11111661.

13. Lazzерini Pietro Enea, Bourjdah Mohamed, Capecci Pier Leopolda. COVID-19, arrhythmic risk, and inflammation. Circulation. 2020;142:7–9. doi:10.1161/CIRCULATIONAHA.120.047293.

14. HCSPI. Provisional statement: Recommendations on prevention and management of Covid-19 in patients at risk of severe forms. Paris: Haut Conseil de la Santé Publique; 2020.

15. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–1720. doi:10.1056/NEJMoa2002302.

16. Eggersmann TK, Degenhardt T, Gluz O, et al. CDK4/6 inhibitors expand the therapeutic options in breast cancer: Palbociclib, Ribociclib and Abemaciclib. BioDrugs. 2019;33:125–135. doi:10.1007/s12249-019-00337-6.

17. Ertl J. Management of adverse events due to cyclin-dependent kinase 4/6 inhibitors. Breast Care (Basel). 2019;14:86–92. doi:10.1111/breasc.12190.

18. Pennault-Llorca F, Dauplat M-H. Les signatures moléculaires des cancers du sein: le point de vue du pathologue. Revue Francophone des Laboratoires. 2011;2011:43–47. doi:10.1177/035511708607-7.

19. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925–1936. doi:10.1056/NEJMoa1607303.
20. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17:425–439. doi:10.1016/S1470-2045(15)00613-0.

21. Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19:904–915. doi:10.1016/S1470-2045(18)30292-4.

22. Zheng J, Yu Y, Durairaj C, Diéras V, Finn RS, Wang DD. Impact of dose reduction on efficacy: implications of exposure-response analysis of Palbociclib. Target Oncol. 2021;16:69–76.

23. Safety and impact of dose reductions on efficacy in the randomised MONALEESA-2, -3 and -7 trials in hormone receptor-positive, HER2-negative advanced breast cancer | British J Cancer. 125:679–686. http://www.nature.com/articles/s41416-021-01415-9.

24. Rugo HS, Huober J, García-Sáenz JA, et al. Management of Abemaciclib-associated adverse events in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: safety analysis of MONARCH 2 and MONARCH 3. Oncologist. 2021;26:e53–e65 Jan.

25. Diéras V, Harbeck N, Joy AA, et al. Palbociclib with letrozole in postmenopausal women with ER+/HER2- advanced breast cancer: hematologic safety analysis of the randomized PALOMA-2 trial. Oncologist. 2019;24:1514–1525 Dec.

26. Spring LM, Wander SA, Zangardi M, Bardia A. CDK 4/6 inhibitors in breast cancer: current controversies and future directions. Curr Oncol Rep. 2019;21. doi:10.1007/s11912-019-0769-3.

27. Ettl J. Management of adverse events due to cyclin-dependent kinase 4/6 inhibitors. Breast Care. 2019;14:86–92. doi:10.1159/000499534.