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PEDIATRIC FUNGAL INFECTIONS (T LEHRNBECHER, SECTION EDITOR)

Clinical Pharmacology of Itraconazole in Children and Adolescents

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Abstract Invasive fungal infections are recognized as life-threatening complications primarily in immunocompromised patients, including children with primary immunodeficiencies and hematological malignancies. The antifungal triazoles have become extremely useful components of the antifungal armamentarium. They are well tolerated and possess a broad spectrum of activity. Itraconazole was discovered in 1984 and became available for clinical use in 1990. Itraconazole is a broad spectrum, triazole antifungal agent, and class II drug molecule with low solubility and high permeability and several indications in adults. This article provides a brief overview of the pharmacology of itraconazole with focus on the available data in immunocompromised children and adolescents.

Keywords Triazoles · Itraconazole · Pharmacology · Children

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Antifungal Triazoles

The antifungal azoles are a class of synthetic compounds that have one or more azole rings and—attached to one of the nitrogen atoms—a more or less complex side chain. Whereas the imidazoles have two, the triazoles have three nitrogen atoms in the five-member ring, which confers improved resistance to metabolic degradation, greater target specificity, and an expanded spectrum of activity [1]. The imidazoles miconazole, and ketoconazole were the first azole compounds developed for systemic treatment of human mycoses. Severe toxicities associated with the drug carrier (miconazole) and erratic absorption and significant interference with the human cytochrome P-450 system (ketoconazole), however, have limited their clinical usefulness [2]. Fluconazole and itraconazole were the first approved antifungal triazoles and have greatly expanded the treatment options upon their introduction in the early 1990s. In the past decade, a new generation of antifungal triazoles has entered clinical practice; these so-called second-generation triazoles include voriconazole, posaconazole, and, still investigational, isavuconazole [3].

Mechanism of Action

Similar to other members of its class, itraconazole inhibits the synthesis of ergosterol, the main predominant sterol in the cell membrane of fungi (Fig. 1). This inhibition specifically interrupts the conversion of lanosterol to ergosterol and leads to accumulation of aberrant 14-alpha-methylsterols and depletion of ergosterol in the fungal cell membrane. These effects alter cell membrane properties and function and, depending on organism and compound, may lead to cell death or inhibition of cell growth and replication. The interaction with structurally similar mammalian cytochrome P-450–dependent enzyme

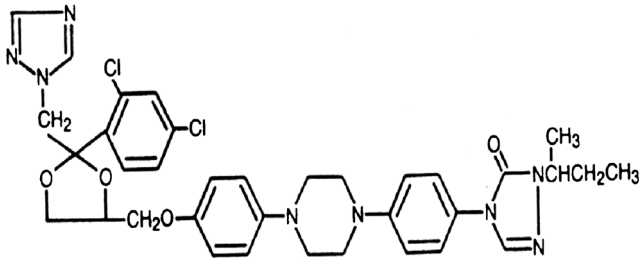

Fig. 1 The chemical structure of itraconazole

systems is responsible for most toxicities and drug interactions of itraconazole and other members of this class of compounds. In addition, the azoles inhibit cytochrome P-450–dependent enzymes of the fungal respiration chain; however, the contribution of this action to their overall activity is unclear [2]. Of note, itraconazole is pharmacologically distinct from other azole antifungal agents in that it has been shown to inhibit both the Hedgehog signaling pathway and angiogenesis [4]. These distinct activities are unrelated to inhibition of the cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase although the exact molecular targets responsible are yet unidentified.

Antifungal Activity

Itraconazole is a useful agent for dermatophytic infections. *Trichophyton* spp., *Microsporum* spp. and, *Epidermophyton* spp. are the most common pathogens [5], and they are generally considered to be fully susceptible to itraconazole. With regards to pityriasis versicolor, all seven recognized species of Malassezia are considered susceptible to itraconazole [6]. Apart from these fungal organisms that are frequent in normal, healthy individuals, itraconazole is generally active against *Candida* spp., *Cryptococcus neoformans*, *Cryptococcus gattii*, *Trichosporon asahii*, and several uncommon yeast organisms, as well as against dimorphic fungi such as *Histoplasma capsulatum*, *Coccidioides* spp., *Blastomyces dermatitidis, Paracoccidioides brasiliensis*, and *Sporothrix schenkii* [1, 7]. It has less activity against *Candida glabrata* and none against *Candida krusei* [2, 8]. Itraconazole also possesses clinically useful activity against *Aspergillus* spp. and dematiaceous molds; however, it is considered inactive against *Fusarium* spp. and the *Mucorales* spp. [2].

Resistance

Antimicrobial resistance is associated with high morbidity and mortality rates in immunocompromised and severely ill hospitalized patients and may be categorized into primary, acquired, and clinical resistance. Several mechanisms of azole resistance in *Candida* spp. have been identified and include, but are not limited to, molecular alterations at the target binding site, increased target expression, and induction of cellular efflux pumps [9•, 10]. Whereas exposure-induced, stable azole resistance has been reported; however, in the clinical setting, azole resistance is encountered most commonly as primary resistance or through selection of primarily resistant subclones during exposure to azoles.

In clinical practice, azole-resistant oropharyngeal and esophageal *Candida albicans* candidiasis has been observed prior to the advent of highly active antiretroviral therapy in azole-exposed patients with advanced HIV infection, and *C. glabrata* and *C. krusei* infections in association with fluconazole prophylaxis in bone marrow transplant and cancer patients [11–13]. Although cross-resistance of *Candida* spp. is common, it is not obligated and patients with fluconazole-resistant mucosal candidiasis may respond to itraconazole or second-generation triazoles [14]. Acquired resistance to azoles has been documented in patients with *C. neoformans* meningoencephalitis [15], and there is an increasing number of reports of secondary azole resistance and azole cross-resistance in filamentous fungi, especially *Aspergillus* spp. [16•, 17, 18]. Azole-resistant aspergillosis was reported in azole-naïve patients, indicating that resistance does not exclusively develop during azole therapy [19].

Pharmacodynamics

In vitro, itraconazole exerts species- and strain-dependent fungistatic or fungicidal pharmacodynamics. Time-kill experiments demonstrated concentration-independent, fungistatic activity of itraconazole against *Candida* spp. and *C. neoformans* [20, 21]. Against *Aspergillus* spp., however, itraconazole displayed time- and concentration-dependent fungicidal activity killing within 24 h of exposure to the drug [22]. Persistent effects have not been reported thus far.

The principal feasibility of a correlation between in vitro susceptibility and outcome was demonstrated in mice with experimental disseminated aspergillosis and in a model of invasive pulmonary aspergillosis in methylprednisolone/cyclosporine-immunosuppressed rabbits [23]. In this model, a significant pharmacodynamic relationship was established between itraconazole concentrations in plasma and antifungal efficacy as a function of the burden of *Aspergillus fumigatus* in lung tissue [24]. In patients, however, the main rationale for monitoring plasma levels has been the erratic oral bioavailability of itraconazole, particularly in neutropenic patients. Historically, the target plasma level for itraconazole has been estimated at 0.25 mg/L by high-performance liquid chromatography (HPLC) at trough [25]. Post-marketing, the predictive value of threshold concentrations of prophylactic itraconazole in adult patients with acute leukemia was found

to be 0.5 mg/L at trough by means of multivariate logistic regression analysis [26•].

Pharmacokinetics

Itraconazole is available as capsules and as oral solution in hydroxypropyl-β-cyclodextrin (HP-β-CD). The parenteral preparation is no longer available in the USA but may be available in other countries. Itraconazole is rapidly absorbed after oral administration. The oral bioavailability of itraconazole is maximal when capsules are taken immediately after a full meal; absorption is reduced in patients taking medications that suppress gastric acid secretion (e.g., H_2-receptor antagonists, proton pump inhibitors) or patients with achlorhydria [2, 27]. Peak plasma concentrations of itraconazole are reached within 1 to 4 h following oral administration. Steady state concentrations are generally reached within about 7 to 14 days [28]. The oral solution of itraconazole in HP-β-CD has improved oral bioavailability that is further enhanced in the fasting state; in adult patients with cancer who were receiving the standard regimen of 2.5 mg/kg of oral HP-β-CD itraconazole twice daily, mean trough levels were 0.8 mg/L under conditions of steady state [29]; systemic absorption of the carrier was negligible [25]. For the intravenous formulation, an alternative dosing schedule has been designed that allows steady-state plasma concentrations to be achieved more rapidly. After administration of the parenteral solution in HP-β-CD, drug and carrier rapidly are dissociated and follow their own disposition; after the recommended regimen of 200 mg twice daily for 2 days followed by 200 mg daily for 5 days, mean trough levels were 0.53 μg/mL. The carrier HP-β-CD was not significantly metabolized, and virtually 100 % was eliminated from plasma within 24 h in unchanged form through glomerular filtration [30] (Table 1).

As a consequence of nonlinear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing [29, 31•]. Most of the itraconazole in plasma is bound to protein (95 %) with albumin being the main binding component. Itraconazole has a large apparent volume of distribution of approximately 11 L/kg and concentrations within tissues such as the lung, kidney, liver, bone, stomach, spleen, muscle, the female genital tract, the skin, and nails are considerable [32, 33]. Itraconazole is metabolized extensively in the liver into a large number of metabolites and is excreted in metabolized form into bile and urine. The major metabolite, hydroxyitraconazole, has antifungal activity comparable to that of itraconazole. It is eliminated more rapidly, but its plasma concentrations at steady state are 1.5 to 2 times higher than those of the parent compound [25]. The elimination half-life of the compound is 20 to 24 h after single dosing and 35 to 40 h under terms of steady state, a finding reflecting saturable excretion mechanisms [34]. As elimination of itraconazole is primarily hepatic, there is no need for dosage adjustment in the presence of renal function impairment [35]. In patients with severe hepatic insufficiency, the elimination half-life of itraconazole can be prolonged, and additional hepatic toxicity or possible drug interactions should be monitored carefully.

For pediatric use, itraconazole oral solution is a significant advance over capsules because children may have difficulty in swallowing tablets, even without the additional complication of mucositis in the case of cancer patients. Furthermore, adjusting the dosages of capsules for children can prove troublesome [36]. Several studies have investigated the pharmacokinetics of the oral HP-β-CD solution of itraconazole in pediatric patients [30, 31•, 36, 37]. In 26 infants and children aged 6 months to 12 years with cancer (n=20) or liver transplantation who received the compound at 5 mg/kg once daily, plasma concentrations were substantially lower than those reported in adult patients with cancer, particularly in children younger than 2 years of age [29, 36]. In another study of 16 neutropenic children (1.7 to 14.3 years of age) who received HP-β-CD itraconazole for antifungal prophylaxis in a split dosing regimen of 2.5 mg/kg twice daily, peak and trough levels of itraconazole were substantially higher; nonetheless, a similar trend toward lower plasma concentrations occurred in the group of children ≤5 years of age [30]. In a cohort of 26 HIV-infected children and adolescents (1.25 to 18 years), HP-β-CD itraconazole was safe and effective for treatment of oropharyngeal candidiasis at dosages of 2.5 mg once a day or 2.5 mg twice daily given for at least 14 days [31•]. Peak and trough levels measured after administration of the split-dosage regimen were similar to those observed in patients with cancer who were receiving the same dosage regimen [30]. Of note, population-based pharmacokinetics in pediatric cystic fibrosis and allogeneic BMT patients receiving the oral solution or the capsule formulation as antifungal prophylaxis, suggest a starting dose of 5 mg/kg twice daily [37]. In a 2-year prospective study carried out in a single pediatric cystic fibrosis center, random itraconazole levels were measured in 16 patients with a median age of 14 years and the aim for a therapeutic range of 5–15 mg/L by bioassay. The mean dose was 5.1 mg/kg/day (range 2.4–8.5). The serum blood levels measured by bioassay suggested that only 2/16 (12.5 %) patients had levels within the therapeutic range [38]. In another study in pediatric cancer pediatric patients, a total of 15 patients (mean age 10.7 years) were studied who received itraconazole as prophylaxis at mean dose of 5.5 mg/kg/day divided in two doses. In this study, 11/15 (73.3 %) patients had mean trough values <0.5 mg/L [39].

Information on the intravenous hydroxypropyl-beta-cyclodextrin formulation is limited to a single-dose pharmacokinetic study in 33 children who received itraconazole at 2.5 mg/kg over 1 h. There was no safety issue, and analysis of pharmacokinetic parameters suggests that the

Table 1 Pharmacokinetics of itraconazole and hydroxy-itraconazole after administration of hydroxypropyl-beta-cyclodextrin oral solution to immunocompromised infants and children

	Children with cancer/liver-TX[1] [n=8, 0.5 to 2 years] 5.0 mg/kg QD ×14 days	Children with cancer[1] [n=7, 2 to 5 years] 5.0 mg/kg QD ×14 days	Children with cancer[1] [n=11, 6 to 12 years] 5.0 mg/kg QD ×14 days	Children with cancer[2] [n=9, 2 to 5 years] 2.5 mg/kg BID ×14 days	Children with cancer[2] [n=6, 6 to 12 years] 2.5 mg/kg BID ×14 days
Itraconazole					
C_{max} [μg/mL]	0.571±0.416	0.534±0.431	0.631±0.358	1.024±0.351	1.524±0.770
T_{max} [h]	1.9±0.1	2.9±2.5	3.1±2.1	n/a	n/a
C_{min} [ug/mL]	0.159±0.218	0.179±0.100	0.233±0.14	0.711±0.251	1.072±0.408
$AUC_{0-\infty}$ [μg/mL h]	6.930±5.83	7.33±5.42	8.77±5.05	n/a	n/a
T ½ beta [h]	47.4±55.0	30.6±25.3	28.3±9.6	n/a	n/a
Acc. factor	6.2±5.0	3.3±3.0	8.6±7.4	n/a	n/a
OH-Itraconazole					
C_{max} [μg/mL]	0.690±0.445	0.687±0.419	0.699±0.234	1.358±0.373	2.180±0.753
T_{max} [h]	4.4±2.3	4.8±2.7	10.8±14.3	n/a	n/a
Cmin [μg/mL]				1.272±0.322	1.964±0.562
AUC_{0-24} [μg/mL h]	13.20±11.40	13.4±9.1	13.45±7.19	n/a	n/a
T ½ beta [h]	18.0±18.1	17.1±14.5	17.9±8.7	n/a	n/a
Acc. factor	11.4±16.0	2.3±1.9	6.4±5.6	n/a	n/a

Pharmacokinetic parameters were obtained after daily dosing over 14 days. All values represent mean values±SD

C_{max} peak plasma levels, T_{max} time until occurrence of C_{max}, $AUC_{0-\infty}$ area under the concentration vs. time curve from zero to infinity, *T½ beta* elimination half-life, accumulation factor (AUC 0–24 day 14/AUC 0–∞ day 1), *n/a* not assessed

compound can be administered by a weight-normalized dosing approach [31•].

Taken together, pharmacokinetic properties of itraconazole in pediatric patients appear not to be fundamentally different from those in adults. A starting dosage of 2.5 mg/kg twice daily of the oral solution can be advocated, based on the available pharmacokinetic data. Trough levels should be monitored, and dosing should be adjusted to maintain plasma concentrations of the parent itraconazole of >0.5 mg/L by HPLC [31•]. In contrast, the use of the intravenous solution cannot be recommended in children and adolescents who are not past puberty.

Adverse Effects

Itraconazole is a relatively well-tolerated drug, and the range of adverse effects it produces is similar to the other azole antifungals [40, 41]. In 189 patients treated for systemic fungal infections at dosages of 50 to 400 mg/day for a median of 5 months, the rate of possibly or definitely related adverse effects was 395 [42]. Most of the observed reactions were transient and included nausea and vomiting (<10 %), hypertriglyceridemia (9 %), hypokalemia (6 %), elevated hepatic transaminases (5 %), rash or pruritus (2 %), headaches or dizziness (<2 %), and pedal edema (1 %). Four percent of patients discontinued itraconazole treatment because of adverse effects. Gastrointestinal intolerance is the dose-limiting toxicity of the oral HP-β-CD formulation. In a comparative study in adult patients with acute leukemia, 46 % of patients receiving a daily dose of 800 mg stopped treatment early because of severe nausea and vomiting. Crossover to the identical dose of the capsule formulation was well tolerated by all patients; patients receiving 400 mg/day of the solution had no gastrointestinal adverse effects [41]. Only a few cases of more severe hepatic injury or hepatitis have been described in literature [43]. Itraconazole can have negative inotropic effects; because of a low but possible risk of cardiac toxicity, itraconazole should not be administered to patients with ventricular dysfunction [44]. Adverse events infrequently reported in all studies included constipation, gastritis, depression, insomnia, menstrual disorders, adrenal insufficiency, gynecomastia, and male breast pain. Rare cases of cardiomyopathy have been reported in adults, but no cases have been described in children [45]. At least one case of anaphylactic shock after long-term intravenous therapy has been reported [46]. Recent data suggest a remarkably high rate of peripheral neuropathy during long-term itraconazole therapy (17 %) [47].

Cyclodextrin itraconazole solution was safe and well tolerated for at least 14 days in reported phase I/II pharmacokinetic studies in immunocompromised pediatric patients [30, 31•, 36]. Vomiting (12 %), abnormal liver function tests (5 %), and abdominal pain (3 %) were the most common adverse effects considered definitely or possibly related to HP-β-CD itraconazole solution in an open study in 103 neutropenic

pediatric patients with cancer who received the drug at 5 mg/kg daily or 2.5 mg/kg twice daily for antifungal prophylaxis for a median duration of 37 days; 18 % of patients withdrew from the study because of adverse events [48]. In another report on pediatric patients with cancer who were receiving prophylactic oral itraconazole, adverse effects that led to the cessation of the itraconazole prophylaxis occurred in 11 % of all 44 courses [49]. Toxicological studies have shown that itraconazole, when administered to rats, can produce skeletal abnormalities. While such toxicity has not been reported in adult patients, the long-term effect of itraconazole in children is unknown [50].

Drug Interactions

There is a long list of drugs known to interact with itraconazole. Itraconazole is a substrate of CYP3A4, but it also interacts with the heme moiety of CYP3A, thus resulting in noncompetitive inhibition of oxidative metabolism of many CYP3A substrates. An interaction also can result from inhibition of P-glycoprotein-mediated efflux, and P-glycoprotein is extensively co-localized and exhibits overlapping substrate specificity with CYP3A [51, 52]. Inhibition of hepatic cytochrome P-450 enzyme systems may lead to increased and potentially toxic concentrations of co-administered drugs. Most important, the coadministration of cisapride, pimozide, bepridil, mizolastine, terfenadine, astemizole, oral midazolam, quinidine, dofetilide, triazolam, sertindole, eletriptan, nisoldipine, and levacetylmethadol with itraconazole can lead to serious cardiac arrhythmias and is thus strictly contraindicated [51–54]. Similarly contraindicated is the coadministration of HMGcoA-inhibitor cholesterol-lowering agents such as atorvastatin, lovastatin, and simvastatin, which are associated with rhabdomyolysis and that of ergot alkaloids metabolized by CYP3A4, which may result in ergotism [51, 55]. Potentially toxic levels of the co-administered drug also can be reached when itraconazole is given along with phenytoin, carbamazepine, benzodiazepines, cyclosporine, tacrolimus, sirolimus, methylprednisolone, budesonide, digoxin, warfarin, sulfonylurea compounds, ritonavir, indinavir, haloperidol, clarithromycin, verapamil, felodipine, busulfan, and vinca alkaloids [51, 54–59]. Increased metabolism of itraconazole resulting in decreased plasma levels can be induced by rifampin, rifabutin, isoniazid, carbamazepine, phenobarbital, and phenytoin [51, 54, 60]. As a consequence, patients who receive itraconazole along with one of the listed drugs should be followed closely, and plasma concentrations of ideally both compounds as well as hepatic function should be monitored carefully.

Clinical Indications

Itraconazole is a useful agent for pityriasis versicolor [1, 61–63], vaginal candidiasis [64], as well as oropharyngeal and esophageal candidiasis [14, 31•, 36, 54]. Regarding tinea capitis, itraconazole (as well as fluconazole and terbinafine) appears to be similar effective and safe as griseofulvin against tinea capitis caused by *Trichophyton* sp.; against tinea capitis caused by *Microsporum* spp., it has similar efficacy and safety as griseofulvin and fluconazole with similar durations of treatment [65, 66]; however, griseofulvin is nowadays not available in certain European countries (e.g., Belgium, Greece, Portugal, and Turkey) [67].

Although the experience with itraconazole in the primary treatment of cryptococcal meningitis is scant, itraconazole has been used with success for long-term treatment of cryptococcal meningitis in patients with HIV infection [68, 69]. Nevertheless, in the recent IDSA guidelines for management of non-HIV-infected, non-transplant hosts with cryptococcal meningitis itraconazole is not suggested for consolidation treatment [70]. As itraconazole is actively removed from the CSF through the blood–brain barrier and has problematic absorbance following oral administration, fluconazole is the first choice regimen for consolidation therapy in immunocompetent children [71]. Itraconazole may be a second-line option for treatment of invasive *Aspergillus* infections, in particular as maintenance or consolidation therapy in non-neutropenic patients [72]. Beyond invasive aspergillosis, itraconazole may be useful in the management of infections by certain dematiaceous molds [73, 74]. Itraconazole appears to be effective in subcutaneous zygomycosis caused by *Basidiobolus ranarum* [75].

Itraconazole has become the first choice for treatment of cutaneous sporotrichosis. However, this recommendation is based on case reports and small series [76]. Itraconazole also has useful clinical efficacy against paracoccidioidomycosis [77, 78] and is effective against nonmeningeal, mild to moderately severe blastomycosis and histoplasmosis in non-immunocompromised patients [42, 79–82], and for induction and maintenance therapy of mild to moderate, nonmeningeal histoplasmosis in HIV-infected patients [82, 83]. Although earlier uncontrolled clinical trials suggested a somewhat inferior efficacy against nonmeningeal and meningeal coccidioidomycosis in comparison to fluconazole [84–86], a randomized, double-blind comparative study in patients with progressive, nonmeningeal coccidioidomycosis showed a trend toward slightly greater efficacy when either of the drugs were given at a daily dosage of 400 mg [87]. Nonetheless, amphotericin B remains the treatment of choice for endemic mycoses in most immunocompromised patients and for those with life-threatening infections [2].

Itraconazole was at least as effective as conventional amphotericin B and was superior with respect to its safety

profile when it was administered as empirical antifungal therapy in persistently neutropenic patients with cancer and in some cases of disseminated *Candida* infection [88•, 89, 90]. Prophylactic itraconazole may reduce the incidence of proven or suspected invasive fungal infections in patients with hematologic malignancies [91, 92] and those patients who have undergone HSCT [93]. Efficacy specifically in the prevention of invasive aspergillosis is supported by a large meta-analysis study [94], but not by a randomized, comparative trial.

Conclusions and Future Perspectives

Although itraconazole has useful pharmacological properties and has been extensively investigated for prevention and treatment of human mycoses in adults, it has never been developed for pediatric patients. Thus, no pediatric label exists to this date and accordingly, any treatment with itraconazole in a patient below 18 years of age may be considered off label.

While insufficient pediatric data exist for the oral tablet and the intravenous formulation, comparatively robust data exist on the pharmacokinetics and the safety of the oral solution formulation in children 2 years and older and in adolescents. For this formulation, a starting dose of 2.5 mg/kg and day may be recommended, followed by therapeutic drug monitoring with individual dose adjustments to achieve and maintain a trough concentration of at least 0.5 mg/L by HPLC. Escalation of exposure to several fold of this target is not advised, as hepatic and other adverse effects are dose-dependent and an upper boundary of target concentrations has never been defined.

Potential indications for use of itraconazole in children and adolescents are vastly restricted to antifungal prophylaxis in immunocompromised patients and patients with chronic destructive lung diseases as treatment experiences, and exposure-efficacy relationships in other indications are virtually unknown and approved alternatives do exist. In recently issued guidelines of the European Conference on Infections in Leukemia (ECIL) [95•], the use of itraconazole, coupled with TDM, is among the primary recommendation for antifungal prophylaxis during the aplastic phase post allogeneic bone marrow transplantation and in patient with acute myeloblastic and recurrent leukemia's, respectively, and it is among the secondary alternative treatments for second-line treatment of invasive aspergillosis [95•].

Compliance with Ethics Guidelines

Conflict of Interest Efi Drogouti, Zoe Dorothea Pana, Athanasios Tragiannidis, Georg Hempel, and Andreas Groll all declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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