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ORAL TOLERANCE INDUCTION TO COTRIMOXAZOLE IN IMMUNOSUPPRESSED PATIENTS WITH A HISTORY OF A NON-SEVERE HYPERSENSITIVITY REACTION

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Background and importance

Cotrimoxazole (CTX) is the first-line therapy for the prevention and treatment of Pneumocystis jirovecii pneumonia (PJP) (Fig. 1). In cases of a previous non-severe hypersensitivity reaction to CTX (Fig. 2), oral tolerance induction using either a single-day or multi-day protocol may be considered as an alternative to more costly therapies such as a pentamidine, dapsone or atovaquone.

Aim and objectives

The aim of this study was to develop a management protocol for oral induction of tolerance to CTX in patients with a history of non-severe hypersensitivity reactions.

Material and methods

Data on CTX hypersensitivity and its management were obtained from published literature, databases (PubMed, Lexicomp, Google Scholar), the Summary of Product Characteristics (SmPC), and expert consultations. The feasibility of oral tolerance induction to CTX for both prophylaxis and treatment of PJP was assessed. Protocols for tolerance induction were proposed, and a list of pharmaceutical excipients in available CTX formulations, was compiled. Patient data on oral CTX tolerance induction were retrieved from two hospitals.

Table 1: A single-day protocol for oral tolerance induction to CTX

Time of drug administration ↑

Hour	Dilution of CTX	Final concentration	Administered amount	The type of used drug brand
5.	160/800 a whole tablet	960 mg	depends on specific strength	CTX different drug brand
4.	undiluted	48 mg/ml	5 ml	Sumetrolim/ CTX oral suspension
3.	1 ml + 9 ml NS	4.8 mg/ml	5 ml	Sumetrolim/ CTX oral suspension
2.	1 ml + 9 ml NS	0.48 mg/ml	5 ml	Sumetrolim/ CTX oral suspension
1.	1 ml + 9 ml NS	0.048 mg/ml	5 ml	Sumetrolim/ CTX oral suspension
0.	1 ml + 9 ml NS	0.0048 mg/ml	5 ml	Sumetrolim/ CTX oral suspension

NS – 0.9% sodium chloride

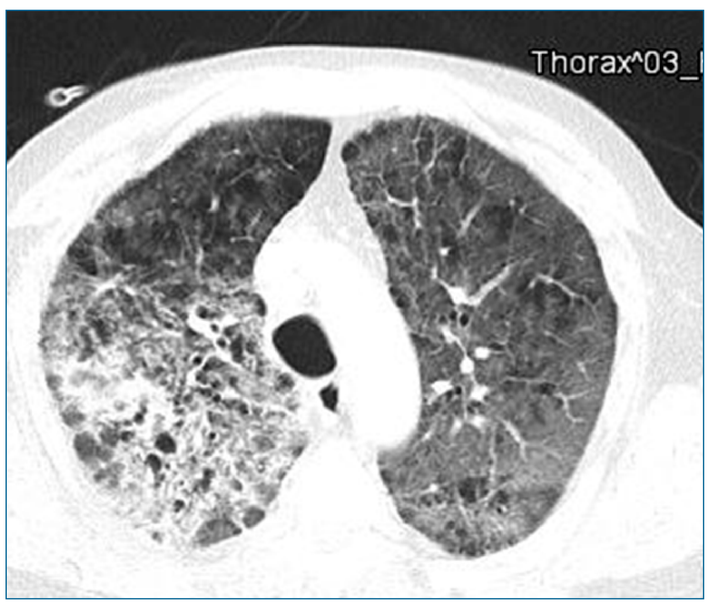
Table 3: The pharmaceutical excipients present in available CTX-containing medications

Pharmaceutical excipient	Biseptol 480 80/16 mg per ml solution for infusion	Cotrimoxazol AL forte 800/160 mg tablet	Biseptol 400/80 mg tablet	Sumetrolim 400/80 mg tablet
Carboxymethylamylum natricum		x		x
Cellulosum microcristallinum		x		
Povidonum		x		
Docusatum natricum		x		
Crospovidonum		x		
Silica coloidalis anhydrica		x		
Magnesii stearas		x	x	x
Solani amylum			x	x
Alcohol polyvinylicus			x	
Methylparabenum			x	
Propylparabenum			x	
Propylenglycolum	x		x	
Talcum			x	x
Gelatina				x
Glycerolum 85%				x
Acidum stearicum 95%				x

Results

- Due to the limited number of relevant publications, and the lack of a standardized protocol, we adapted both single-day and multi-day protocols from existing studies.
- The single-day protocol (Gluckstein et al.[1]) is suitable for patients with non-severe skin reactions. In collaboration with the hospital pharmacy, a dilution protocol for Sumetrolim oral suspension was developed (Tab. 1). Broyles et al.[2] recently recommended shorter intervals between doses.
- The multi-day protocol (Tab. 2, adapted from Absar et al.[3]) is used for more severe reactions and can also be applied in outpatient settings for non-severe cases.
- Protocol selection must be strictly individualized based on patient condition and reaction severity. Severe reactions require basophil activation and skin tests, followed by an oral provocation test with a full therapeutic CTX dose under one-hour observation, with readiness to manage anaphylaxis (adrenalin 300-500 mcg i.m.).
- A list of CTX product excipients was compiled (Tab. 3), revealing that generic substitution may improve tolerance.
- Alternative preparations were proposed by pharmacists during Sumetrolim oral suspension shortage to ensure optimal desensitization dosing (Fig. 3).
- To prevent tolerance loss during PJP prophylaxis, especially after dose interruptions longer than three days, CTX is recommended to be administered three times a week, every other day, or daily. Oral induction is contraindicated in severe delayed-type hypersensitivity reactions, Stevens-Johnson syndrome, or acute generalized exanthematous pustulosis. In such cases, the alternative therapies must be prescribed.
- Since the implementation of the local protocol, nine immunocompromised patients were successfully delabeled from CTX allergy through oral desensitization or generic substitution (Tab. 4)
- A standardized process for managing patients with a history of CTX allergy was established at the UH HK (Fig. 4).

Figure 1: CT image of PJP (Department of Pulmonary Medicine, University Hospital Hradec Králové)



Conclusion and relevance

The prevalence of hypersensitivity reactions to CTX in general population is lower than reported in patient's medical history. There is no standardized protocol that is universally recognized as the the most effective or least hazardous. Multidisciplinary collaboration is essential for the rational treatment and effective prophylaxis of PJP infections.

References

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Table 2: A multi-day protocol for oral tolerance induction to CTX

Day	Dose of Sumetrolim oral suspension 4 mg/0.8 mg/ml	CTX in mg
1.	0.25 ml	1.2
2.	0.5 ml	2.4
3.	1 ml	4.8
4.	2 ml	9.6
5.	5 ml	24
6.	10 ml	48
7.	15 ml	72
8.	20 ml	96
9.	25 ml	120
10.	50 ml	240
11.	Start taking CTX tablet 480 mg daily	
12.	Continue CTX tbl 960 mg tablet three times a week, after meal, sun protection needed	

Figure 2: Clinical manifestations of CTX toxicity, grade 1-4 (adapted from Buttigieg et al., 2017[4])

1. Erythema
2. Diffuse maculopapular rash, dry desquamation
3. Vesiculation, mucosal ulceration
4. Exfoliatie dermatitis, Stevens-Johnson syndrome or erythema multiforms, moist desquamation, acute generalized exanthematous pustulosis

Figure 3: The formula for a multi-day protocol and an adapted formula for alternative preparation during Sumetrolim oral suspension shortage

Sumetrolim „desensitizing" oral solution *4 mg/0.8 mg/1 ml solution (130 ml)*

Sumetrolim 48 mg/ml	*13 ml*
Inf. natrii chlorati 0.9%	*117 ml*
M.f. sol.	

Expiration date: 14 days
Storage conditions: 15-25 °C
Shake well before use!

Susp. cotrimoxazoli 48 mg/ml

Cotrimoxazol AL forte 960 mg tbl	*V (quinque)*
Syrspend SF PH4 liquid	*ad 100 ml*

M.f. susp.
Expiration date: 28 days
Storage conditions: 2-8 °C
Shake well before use!

Figure 4: The process of multidisciplinary collaboration at the University Hospital Hradec Králové

Table 4: Selected case studies of oral tolerance induction to CTX

Protocol	Case studies
A multi-day	Male, 51 years old, newly diagnosed with acute T-ALL in 05/2022, **AA: Biseptol tbl – unspecified skin reaction, delayed type**, occurred recently during treatment, infection prophylaxis for PCJ with dapsone 100 mg/day, after induction, switched to Cotrimoxazol AL forte 960 mg 1-0-1 twice weekly, patient monitored at the UH HK.
	Male, 80 years old, diagnosed with relapse of MM 07/2022, **AA: Cotrimoxazol AL forte tbl – generalized rash, delayed type**, infection prophylaxis for PCJ with 100 mg/day of dapsone, after induction switched to Biseptol 480 mg 3 times a week, 2 tablets, monitored at the UH HK.
	Male, 39 years old, diagnosed with APL 06/2015, **AA: Biseptol tbl, Cotrimoxazol AL forte tbl – skin form, delayed type**, condition after severe allergic reactions following the administration of blood transfusion products prior to allogeneic hematopoietic stem cell transplantation, in prophylaxis of PCJ infection with inhaled pentamidine 300 mg/month, after induction Biseptol 480 mg tbl 1-0-0 daily. **An escalation protocol** was used with undiluted Sumetrolim syrup every 12 hours: D1 0.1 ml-0-0.2 ml, D2 0.4 ml-0-0.8 ml,D31.6 ml-0-3.2 ml, D4-D5 6.4 ml-0-6.4 ml, D6 6.4 ml-0-Biseptol 480 mg tbl, D7 and onwards, continuing Biseptol 480 mg tbl 1-0-0 for PCJ prophylaxis, monitored at ÚHKT.
A single-day	Female, 53 years old, diagnosed with right breast cancer, nosocomial pneumonia of combined etiology (due to nausea and vomiting, the patient self-medicated with dexamethasone): COVID-19 infection, pulmonary aspergillosis, CMV pneumonia, PJP, **AA: Biseptol tbl – past history of skin rash**, treatment of PJP with trimethoprim 200 mg tablets 2-2-2-2 + dapsone 100 mg/day, after induction, parenteral Biseptol was administered at therapeutic doses, then switched to oral Cotrimoxazol AL forte tbl without any issues, monitored at the UH HK.

T-ALL – Acute T-lymphoblastic leukemia, **MM** – Multiple myeloma, **APL** – Acute promyelocytic leukemia, **AA** – Allergic anamnesis, **PCJ** – Pneumocystis jirovecii, **PJP** – Pneumocystis pneumonia, **CMV** – Cytomegalovirus, **TBL** – tablet, **UH HK** – University Hospital Hradec Králové, **ÚHKT** - Institute of Haematology and Blood Transfusion

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