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Drug-induced hair colour changes

Hair colour modifications comprise lightening/greying, darkening, or even a complete hair colour change, which may involve the scalp and/or all body hair. Systemic medications may cause hair loss or hypertrichosis, while hair colour change is an uncommon adverse effect. The rapidly increasing use of new target therapies will make the observation of these side effects more frequent. A clear relationship between drug intake and hair colour modification may be difficult to demonstrate and the underlying mechanisms of hair changes are often unknown. To assess whether a side effect is determined by a specific drug, different algorithms or scores (*e.g.* Naranjo, Karch, Kramer, and Begaud) have been developed. The knowledge of previous similar reports on drug reactions is a key point of most algorithms, therefore all adverse events should be recognised and reported to the scientific community. Furthermore, even if hair colour change is not a life-threatening side effect, it is of deep concern for patient's quality of life and adherence to treatment. We performed a review of the literature on systemic drugs which may induce changes in hair colour.

Key words: hair colour changes, hair depigmentation, hair hyperpigmentation, drug

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Hair colour changes may occur in a variety of cutaneous and internal organ diseases, and include lightening/graying, darkening or even a completely new colour, involving the scalp, eyelashes, eyebrows, moustache, or all body hair. Hair darkening has been described in Addison's disease, neurodermatitis, and porphyria cutanea tarda, while hair lightening has been associated with hyperthyroidism, acute extensive alopecia areata, vitiligo, and genetic disorders such as Werner syndrome, ataxia-telangiectasia, and Waardenburg syndrome [1]. Systemic medications frequently cause hair loss or hypertrichosis, while hair colour changes are an uncommon drug-induced adverse event. Both hair hyperpigmentation (darkening of the original colour or repigmentation of grey hair in older people) and hypopigmentation (lightening, bleaching, graying or reddening) or a completely new hair colour have been described after drug administration [1]. The underlying mechanisms of drug-induced hair colour changes are not clear and the relationship between drug intake and colour modification is often difficult to prove. In clinical practice, the widely used estimation tool to assess adverse drug reactions (ADRs) is the algorithm which consists of a series of queries, each with a defined score, in order to quantify the probability of a cause and effect correlation [2]. The algorithms are simple tools to assess causality, however, unfortunately, although they demonstrate good specificity, they also demonstrate poor sensitivity [3, 4]. During the last 30 years, several algorithms as evaluation tools were developed, such as Karch algorithm [5], Kramer algorithm [6], Begaud algorithm [7], and WHO-UMC (WHO-UMC causality assessment) [8], but none of these are unanimously acknowledged as a foolproof tool; indeed, evaluation of the same drug reaction using different algorithms showed significantly variable results [3, 4]. Naranjo's algorithm [9] is a simple and brief ADR evaluation tool which has been shown to increase significantly the intra-rater agreement (between a panel of expert dermatologists) from 57% to 97%, as compared to clinical judgment alone [4]. Therefore, the high specificity of the Naranjo score makes this algorithm a tool widely used by pharmacovigilance centres in several countries [4]. However, the Naranjo's algorithm is not recommended in the evaluation of ADRs in children because of its poor reliability [10]. The Naranjo score consists of a series of ten questions, each scored with a point value ranging from -1 to +2 (maximum score=13). The final score corresponds to a probability scale ($\geq$9: very probable; 5-8: probable; 1-4: possible; $\leq$0: dubious). The knowledge of previous conclusive reports on drug reactions is a key point of most causality algorithms. We performed a literature review on drug-induced hair colour changes since 1948 to date, by entering on Pubmed and Google Scholar the terms "hair colour changes", "drug hair changes", and "hair changes". The hair colour before and after drug administration was described in detail according to the description reported in the original article, although in most cases, the terms "depigmentation/hypopigmentation" and "hyperpigmentation" have been used to define hair lightening and darkening, relative to the original colour, respectively. In these cases, we have faithfully retained the terms reported in the original articles. The data is summarised in *table 1* .

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Table 1. Systemic drugs that induce hair colour changes.

Drug	Dosage (range)	Hair colour change (no. of cases reported)	Period of occurrence (no. of months)	Reversible after treatment	Associated pigmentary skin changes (no. of cases reported)	References
Chloroquine Hydroxychloroquine	100-1,250 mg/daily 400-2,000 mg/daily	Depigmentation (27) Depigmentation (4)	1-12 3-4	Yes (18)-N/A (9) Yes (1)-N/A (1)	Hypopigmented maculae (1) No	11-23 24-25
Imatinib	≥300 mg/daily	Hyperpigmentation/Re-pigmentation of grey (10) Depigmentation (2)	1-14	Yes (1)-N/A (11)	Hyperpigmentation (1) Hypopigmentation (1)	28-31
Sunitinib	≥50 mg/daily	Depigmentation (79)	1-5	Yes (40)-N/A (39)	Yellowish facial discolouration (N/A)	52-60
Pazopanib	300-2,000 mg/daily	Depigmentation (272)	2	Yes (21)-N/A (251)	Hypopigmentation (37) Hyperpigmentation (1)	64-70
Dasatinib	100-200 mg/daily	Depigmentation (4)	1-6	Yes (1)-N/A (3)	Hypopigmentation (2)	71-74
Valproate	70 mg/kg/daily-1,000 mg/daily	Depigmentation (2) Hyperpigmentation (1) Generic colour changes (5)	5-10	Yes (1)-No (1)-N/A (6)	No	75-78
Phenytoin	N/A	Depigmentation (1)	N/A	N/A	Lyell syndrome (1)	80
Phenorbital	N/A	Depigmentation (1)	2	No	Toxidermia (1)	81
Cyclophosphamide, bleomycin, CCNU	N/A	From red to black (1)	N/A	N/A	No	1
Cyclophosphamide, adriamycin, 5-FU	N/A	From blond to dark brown (1)	N/A	No	No	1
Vincristine, bleomycin, doorubicin	N/A	From black to red (1)	N/A	No	No	1
Vincristine	N/A	From black to red (1)	N/A	N/A	No	1
Tamoxifen	N/A	Depigmentation (1)	N/A	N/A	No	82
Cisplatin		Depigmentation (3) Hyperpigmentation (11) Generic colour changes (5)	N/A	N/A	No	83
Interferon low dose	3.000.000 UI/3 times/week	Depigmentation (6)	N/A	Yes (N/A)	No	84-85
Cyclosporine	2.5 mg/kg/daily	Hyperpigmentation (2)	2	N/A	No	86-87
Acitretin	3 mg/kg/daily	Depigmentation (1) Hyperpigmentation (2)	6-12	N/A	No	84
Etretinate	0.5 mg/kg/daily	Depigmentation (1) Hyperpigmentation (1)	9	N/A	N/A	88
Indinavir	N/A	Hyperpigmentation (N/A)	N/A	N/A	No	1, 84
Zidovudine	N/A	Hyperpigmentation (N/A)	N/A	N/A	No	1, 84
Verapamil	240 mg/daily	Hyperpigmentation (1)	12	N/A	No	1, 84
P-aminobenzoic acid	200 mg-24 g/daily	Hyperpigmentation (4)	2-12	N/A	No	1
Mephesin	5-12 g/daily	Depigmentation (4)	3-4	Yes (N/A)	No	1
Propofol	140 mg once	From blond to green (1)	2 days	Yes (1)	No	89

Abbreviations: N/A= not available

Drugs that induce hair colour changes

Chloroquine

Chloroquine (CHL) is an antimalarial drug approved by both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of lupus erythematosus and rheumatoid arthritis. Lightening on the hair scalp, and less frequently on the eyelashes, eyebrows, moustache and body hair, has been shown to be induced by CHL administered at a dosage starting from 250 mg daily [11-23]. Hair hypopigmentation (a brightening of any hair colour leading to whitening) occurred from four weeks up to 12 months after treatment initiation, and was reversible after discontinuation or dosage reduction. Hair hypopigmentation has been also described after hydroxychloroquine administration [24, 25], but a revert to normal hair colour occurred when CHL was switched to hydroxychloroquine [15, 16, 20]. Skin hypopigmented maculae associated with hair depigmentation have been rarely reported [18]. The pathophysiological mechanism of hair and skin hypopigmentation during CHL treatment is not fully understood, but previous studies showed remarkable affinity of CHL for those tissues which have abundant melanin content, such as the skin and eyes [26]. Hypopigmentation was indeed more common in patients with blond, light brown, or red hair, suggesting a greater interaction between CHL and pheomelanin rather than eumelanin [21]. However, even subjects with darker hair may experience hair lightening [13, 14, 17].

Tyrosine kinase inhibitors (TKI)

The c-kit signalling pathway is primed by the ligand stem cell factor (SCF), and is known to be involved in melanogenesis, as well as hair pigmentation, through the downstream activation of MAP kinase Erk-2 and phosphorylation of microphtalmia transcription factor [27]. SCF/c-kit interaction during early anagen is a key event for normal pigment production. In most cases, the hair depigmentation due to c-kit inhibitors is reversible after treatment discontinuation, suggesting that these drugs might determine a temporary dysfunction of melanocytes rather than having a cytotoxic effect. It is not completely clear why c-kit inhibitors may cause both hypo- and hyperpigmentation. Indeed, the different effects of c-kit inhibitors on hair pigmentation could be explained by the inhibiting activity of these drugs on other receptors, such as vasoactive endothelial growth factor receptor (VEGFR) or platelet-derived growth factor receptor (PDGFR) [28].

Imatinib

Imatinib is an oral TKI approved by FDA and EMA for the treatment of chronic myeloid leukaemia (CML), gastrointestinal stromal tumour (GIST), metastatic dermatofibrosarcoma protuberans (DFSP), and other chronic myeloproliferative diseases (*i.e.* chronic eosinophilic leukaemia and myelodysplastic syndrome). Imatinib inhibits BCR-ABL, PDGFR, and c-kit. Both hair depigmentation (lightening) [28, 29] and hair darkening (repigmentation of grey hair) [30, 31] have been reported during imatinib treatment at a dosage of 300-800 mg daily, with onset occurring after a median time of four weeks (range: 1-14 months) following treatment initiation. In the majority of cases, the pigmentary abnormalities were reversible after dose reduction or drug withdrawal. Localized or diffuse skin depigmentation has been observed in 15-25% of patients [32-48], and cases of cutaneous [31, 32, 37, 44, 45], nail [40, 42, 47], or gingival [42, 43, 47] hyperpigmentation have been described. The fact that such adverse events are relatively frequent and dose-dependent suggests that they are due to a direct pharmacological effect of imatinib. C-kit receptors are widely expressed in different types of tissues and cells (*i.e.* hematopoietic stem cells, mast cells, and melanocytes) and different isoforms of c-KIT exist as a result of alternate mRNA splicing events. The minor sequence differences between the c-KIT isoforms might be correlated to differences in signalling activation and biological behaviour [49].

Sunitinib

Sunitinib is an oral TKI approved by the FDA and EMA to treat metastatic renal cell carcinoma, pancreatic neuroendocrine tumours, and imatinib-resistant GIST. Sunitinib has demonstrated direct antiproliferative and antiangiogenic activity by inhibiting PDGFR, VEGFR, Fms-like tyrosine kinase-3 (FLT-3) receptor, and c-kit. Hair depigmentation (bleaching or graying) on the scalp, eyebrows, eyelashes, or body hair is a dose-dependent side effect reported in 7-14% of patients treated with sunitinib at a dosage of 50 mg daily [50, 51] and in up to 64% of patients receiving >50 mg daily [52-60]. Hair depigmentation occurred between Week 1 and week 18 of treatment; in all cases, it was reversible within two to three weeks after treatment discontinuation. Alopecia has been shown to occur in 6% of patients receiving sunitinib, and the hair that may regrow is more brittle, curly, and pigmented than the patient's original hair [47]. In addition, yellowish facial discolouration has been described after dosage of at least 50 mg/die of sunitinib [53, 55, 57, 59].

Sorafenib

Sorafenib has been approved by FDA and EMA for the treatment of locally recurrent or metastatic thyroid carcinoma refractory to radioactive iodine treatment, renal cell carcinoma, and hepatocellular carcinoma. Sorafenib targets VEGFR 1-3, BRAF, and REarranged during Transfection (RET) tyrosine kinase, inhibiting the proliferation and angiogenesis of tumour cells. Alopecia has been reported in up to 27% of patients receiving sorafenib [52], from two to 16 weeks after treatment initiation. Hair may regrow even while patients are still receiving sorafenib, although the hair is usually more brittle and curly or, occasionally, more pigmented than that before treatment [52]. Only one case of generalized skin depigmentation has been described in association with hair loss during treatment with sorafenib (800 mg daily) [61]. Hair loss might be due to the inhibition of VEGFR since it has been shown that in the anagen phase, VEGF is able to increase hair growth and diameter [62], while the change in hair texture might be associated with inhibition of PDGFR, which regulates the duration of

the anagen phase. In addition to the c-kit pathway, PDGFR has also been implicated in skin melanocyte development and proliferation [63].

Pazopanib

Pazopanib is an oral selective TKI which has been approved by the FDA and EMA for the treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma. Pazopanib inhibits angiogenesis and tumour growth by targeting VEGFR 1-3, PDGFR-alfa-beta, and c-kit. Reversible hair depigmentation has been demonstrated in 32-44% of patients treated with pazopanib [64-70], sometimes associated with skin hypopigmentation [64, 67-69], while only one case of skin hyperpigmentation has been described so far [68]. A reversible hair depigmentation usually occurs within the first two months of treatment, with involvement of both scalp and body hair [67].

Dasatinib

Dasatinib is an oral TKI, approved by the FDA and EMA, as first-line treatment for CML Philadelphia chromosome-positive in the chronic phase, and as second-line treatment for CML in the chronic, accelerated or blast phases, as well as for Philadelphia chromosome-positive acute lymphoid leukaemia. Dasatinib has a wide spectrum of inhibitory effects, including inhibition of bcr-abl, src family kinase, and, to a lesser degree, c-kit, PDGFR, and ephtin A receptor kinases. A few cases of hair depigmentation have been reported during dasatinib treatment, probably due to the lower affinity of the drug for c-kit and PDGFR, as well as to a less common administration of this drug compared to other c-kit inhibitors, such as imatinib and pazopanib. Both isolated hair depigmentation [71-73] and associated vitiligo-like [72] skin patches have been described using $\geq$100 mg daily of dasatinib. This effect was fully reversible; it was lost when anti c-kit treatment was discontinued and reacquired when treatment was restarted [74].

Antiepileptics and anticonvulsivants

Valproic acid (VPA)

VPA is a widely used antiepileptic drug, approved by the FDA and EMA for seizures and maniac-depressive disorder, which has pleiotropic effects on the g-amino-butyric acid receptor, as well as on membrane conductance, metabolic pathways, and the fatty acid composition of membranes. Dose-dependent, reversible hair loss has been shown in up to 20% of long-term users of VPA, while changes in hair colour and/or hair structure have been rarely reported [75-78]. Both bleaching (from black or brown to blond hair) [76, 78] and darkening of the hair (from blond to dark hair) [77] on the scalp have been described after 5-10 months of treatment with VPA. No skin colour changes have been documented. Some authors suggest a significant correlation between VPA dosage and detection of VPA in hair, furthermore VPA concentration seems to be higher in dark/brown rather than blond/grey hair [79].

Phenytoin and phenobarbital

Phenytoin and phenobarbital are anticonvulsant drugs used in the management of partial seizures and tonic-clonic seizures. Hair depigmentation has been described in one patient after toxic epidermal necrolysis due to phenytoin [80], and skin and hair depigmentation (from black to blond hair) in another patient after Lyell's syndrome due to phenobarbital [81]. It is still not clear whether the depigmentation might be due to the direct cytotoxicity of the anticonvulsants to melanocytes. Some evidence showed that phenytoin concentration in hair scalp is dose-dependent and is related to patients' hair colour, such that black and brown hair have significantly higher levels compared to either blond or grey hair [79].

Other drugs

Hair loss is one of the most common side effects of antineoplastic drugs and hair regrowth is usually very fast after treatment discontinuation, although in some cases, hair shape and colour may be different. Post-alopecia regrowth of hair with both lighter or darker colour has been shown with *cisplatin* [1], while hair darkening has been reported with *tamoxifen*, *busulfan*, *cyclofosfamide,* and *antimetabolites* [1, 82, 83]. The information about specific chemotherapeutic agents is limited and based on case reports.

Reversible hair whitening and changes in hair shape have been reported in up to 18% of patients treated with low doses of *interferon-a*. An MHC-related cytotoxic T-cell activity against melanocytes is believed to be the underlying causative mechanism [84, 85].

Hypertrichosis is a well-known, dose-related side effect of *cyclosporine* (Cs), occurring in up to 50% of transplant patients who take high dosages of the drug, and rarely (3%) in patients affected by skin disease and treated with a maximum of 5 mg/kg daily [84]. Two cases of hair darkening induced by Cs have been described, suggesting that Cs may promote the production of growth factors or cytokines which are capable of stimulating tyrosinase activity [86, 87].

Sporadic cases of hair whitening/discolouration or darkening have been described with vitamin A derivatives, such as *acitretin* [84] and *etretinate* [88]. Isolated cases of hair darkening with *indinavir*, *zidovudine,* and *verapamil* [1, 84], hair discolouration with *mephesin,* and reversals from grey to the original hair colour with *p-aminobenzoic acid* have been reported [1]. Additional hair colour changes include reversible changes from light brown to green in both pubic and scalp hair [89].

Discussion

The exact mechanism of drug-induced hair colour changes is not completely known for most of the currently used medications. To establish the relationship between drug intake and hair colour modification, it is important to review the patient's complete medical history and consider all drugs taken by the patient up to one year before the onset of the colour change [84]. Furthermore, the knowledge of previously reported cases of ADRs is crucial in order to use causality algorithms [5-9]. Once the causative role of a specific drug in hair colour modification is suspected or proven, the case should be reported to the dermatology

community. The increasingly long-term administration of new drugs, such as kinase inhibitors, in patients with various malignancies makes the observation of these side effects more likely in clinical practice. There is evidence that the occurrence of skin toxicity may cause dose delays, dose reductions, or even treatment discontinuation in patients treated with chemo/radiotherapy [90]. Thus, ADRs occurring on the skin, hair, and appendages should be recognised early, and extensively discussed with patients in order to maintain patients' adherence to treatment and their quality of life during treatment while ensuring clinical benefit. ■

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