Chapter 8

Insight in taste alterations during treatment with protein kinase inhibitors

Anne van der Werf
Maria Rovithi
Jacqueline A.E. Langius
Marian A.E. de van der Schueren
Henk M.W. Verheul

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Abstract

The role of Protein Kinase Inhibitors (PKI) in the treatment of various types of cancer is increasingly prominent. Their clinical application is accompanied by the development of side effects, among which patient-reported taste alterations. These alterations are missed frequently, but impair nutritional intake, are associated with weight loss and often result in significant morbidity, especially in the context of chronic administration. Accurate reporting of taste alterations is hampered by lack of modules for symptom objectification and inadequate understanding on the underlying mechanisms. In this review we initially describe the physiology of taste and smell and the mechanism of action of PKIs. We proceed to summarize taste related side effects as reported in major clinical trials and describe possible causal factors. Lastly, an in-depth analysis is given on potential molecular pathways responsible for the PKI-induced taste alterations. Objectification of patient-reported symptoms and universal reporting, along with a better understanding of the underlying mechanisms, will lead to early recognition and optimized treatment, ultimately improving patient adherence and quality of life.

Keywords: Protein kinase inhibitor; dysgeusia; dysosmia; taste; smell; oral adverse events; mucositis
Introduction / background

In the last decade, our increasing insight in the underlying biology of tumorigenesis has revealed distinct pathways that support tumor growth and sustain angiogenesis. Precision blockade of these pathways leads to increased tumor vulnerability and provides the scientific rationale for the development of targeted agents. Protein kinase inhibitors (PKIs) constitute a paradigm category of this class of anticancer agents that act by blocking the intracellular kinase domain of growth receptors or intracellular kinases, thereby inhibiting downstream signaling. Several PKIs have supplanted long-established chemotherapeutic agents and have been approved as standard of care in various treatment lines in the disease course. Clinical application showed their potential to improve patient survival and induce long term disease stabilization in a variety of tumor types. Despite the initial expectations of exclusive tumor cell specificity as opposed to conventional chemotherapeutics, adverse events have been increasingly reported. Chronic administration and subsequent prolongation of survival make the recognition and treatment of these side effects throughout the treatment period imperative, in order to maintain an appropriate risk/benefit ratio.1-4

One of the most commonly reported side effects of PKIs is taste alteration, often referred to as dysgeusia. Taste alterations impair nutritional intake and influences quality of life in patients with cancer.5-8 Reporting of this side effect is usually limited to subjective descriptions of alterations; taste function has never been objectively assessed in patients receiving PKIs. The reported prevalence of PKI induced patient-reported taste alterations varies depending on the type of PKI and treatment dose (table 1). Examples include sunitinib, a Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitor, with a prevalence of patient-reported taste alterations varying from 18%9 to 63%10 and vismodegib, a Hedgehog signaling pathway inhibitor, with a reported prevalence varying from 19%11 to 85%.12

The course of taste alterations has been described in a few studies. Development of oral adverse events were described to develop in 1 to 15 weeks after introduction of sunitinib or sorafenib.13 In the majority of patients treated with vismodegib, patient-reported taste alterations developed within the first month after initiation and reversed within one month after discontinuation of treatment.12

Although data on prevalence and the course of patient-reported taste alterations have been reported, more detailed data remain limited. The nature of the these alterations is not consistently described and may involve taste loss or taste hypersensitivity, as well as taste alteration, including a metallic, bitter, sour or salty taste.5 Furthermore, the potential contribution of concurrent smell alterations has been inadequately recognized and
recorded. This may be caused by the inconsistency among different trials in recording, reporting and scoring of patient-reported taste alterations while discrepant terminology further smothers the exact prevalence.\(^4\) In addition, there are no consensus recommendations regarding objectification and monitoring of the symptoms. Simultaneously with lack of routine objectification of described symptoms, effort dedicated to unravelling the underlying pathobiology remains limited. Nevertheless, the different manifestations, symptoms, clinical presentations and treatment of oral side effects caused by targeted agents compared to ‘traditional’ chemotherapy, hint at the possibility of different pathobiology.\(^\text{14}\) Inadequate understanding on the underlying pathobiology further restrains the identification of optimal treatment options.\(^5,\text{14,15}\) The aim of this article is to provide insight in potential mechanisms of PKI induced patient-reported taste alterations. First the physiology of flavor perception is described, as well as the mechanism of action of PKIs, followed by working hypotheses on the molecular pathways underpinning the development of patient-reported taste alterations in patients treated with PKIs.

\textbf{Table 1} Examples of PKIs and reported prevalence of patient-reported taste alteration

<table>
<thead>
<tr>
<th>PKI</th>
<th>Primary target(^16)</th>
<th>Daily dose</th>
<th>Prevalence taste alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{Imatinib}</td>
<td>ABL, KIT, PDGFR</td>
<td>400 mg</td>
<td>3-13%(^\text{17,19})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg</td>
<td>14%(^\text{17})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800 mg</td>
<td>NR</td>
</tr>
<tr>
<td>\text{Dasatinib}</td>
<td>ABL, Src</td>
<td>100 mg</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>140 mg</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>\geq 200 mg</td>
<td>3-10%(^\text{20})</td>
</tr>
<tr>
<td>\text{Erlotinib}</td>
<td>EGFR</td>
<td>150 mg</td>
<td>6%(^\text{21})</td>
</tr>
<tr>
<td>\text{Gefitinib}</td>
<td>EGFR</td>
<td>250 mg</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg</td>
<td>10%(^\text{22})</td>
</tr>
<tr>
<td>\text{Osimertinib}</td>
<td>EGFR</td>
<td>80 mg</td>
<td>NR</td>
</tr>
<tr>
<td>\text{Sunitinib}</td>
<td>KIT, VEGFR, FLT3</td>
<td>37.5 mg</td>
<td>20%(^\text{9,10,23-27})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg</td>
<td>18-63%(^9,10,23-27)</td>
</tr>
<tr>
<td>\text{Sorafenib}</td>
<td>VEGFR, BRAF</td>
<td>800 mg</td>
<td>3-55%(^26,28-32)</td>
</tr>
<tr>
<td>\text{Vismodegib}</td>
<td>SMO</td>
<td>150 mg</td>
<td>19-85%(^11,12,33-35)</td>
</tr>
<tr>
<td>\text{Crizotinib}</td>
<td>ALK, c-Met, ROS1</td>
<td>500 mg</td>
<td>11-26%(^36-38)</td>
</tr>
</tbody>
</table>


Taste versus flavor
Taste is a chemical sense that evaluates the nutritious content of food and prevents ingestion of potentially toxic substances. The detection of the five different taste qualities (sweet, bitter, salty, sour and umami) by taste bud receptors in the oropharynx and tongue results in the sense of taste. However, this sense is frequently confused with ‘flavor’, which refers to the sense produced after integration of both taste and smell in the brain and is related to temperature and tactile information. Thus, whereas taste specifically refers to taste information arising from taste bud receptors, flavor refers to the end result after the convergence of information from multiple senses in the brain. An overview of how the sense of taste and smell are processed and integrated in the brain to produce the sense of flavor is shown in figure 1. Because smell is an important contributor to flavor, smell alterations are often reported by patients as taste alterations. Therefore, patient-reported ‘taste alterations’ may be caused by taste and/or smell changes. The physiology of both sensory systems is described below.

**Physiology of taste**

**Signal transduction**

Perception of taste starts when tastants interact with taste buds. Each taste bud consists of different morphological cells: type I cells are considered to be supporting cells which are wrapped around other cell types and orchestrate reuptake or degradation of neurotransmitters; type II are taste receptor cells for sweet, bitter and umami; type III are taste receptor cells that appear to be sour and possibly salty detectors, although the cells type(s) mediating salty taste remains ambiguous. Every taste quality is mediated by a specific receptor, while signal transduction cascades are similar for specific cell types. Type II cells contain receptors for sweet, bitter or umami, which are specific G protein coupled receptors. The intracellular transduction cascade is mediated, among others, by phospholipase Cβ2 (PLC-β2) and inositol-trisphosphate (IP3). After depolarization of the taste receptor cell, the taste signal is transmitted to sensory nerves, in which adenosine triphosphate (ATP) is the key neurotransmitter. Type III cells possess specific ion-channels. Direct entry of the ion generates a positive inward current and additional depolarization results in signal transduction to sensory nerve fibers, using 5-HT and noradrenalin as neurotransmitters. The signal transduction of each taste quality, including the involved neurotransmitters, is shown in detail in figure 2.
Figure 1 Integration of taste and smell into flavor perception and potential mechanisms in which protein kinase inhibitors may influence flavor processing.

Shown in black: Taste and smell are processed via distinct receptors, cranial nerves and brain regions. The orbitofrontal cortex is the first place where taste and smell information converges and, together with temperature and texture, underlie the sense of flavor.\textsuperscript{40,42} Shown in grey: Mechanisms in which protein kinase inhibitors may interfere with the sense of taste or the sense of smell, thereby causing an altered flavor perception. cAMP: cyclic adenosine monophosphate. CaMKII: Ca\textsuperscript{2+}/calmodulin kinase II. DAG: diacylglycerol. EGFR: epidermal growth factor receptor. FGFR: fibroblast growth factor receptor. FLT3: fms-like tyrosine kinase receptor-3. IP\textsubscript{3}: inositol-trisphosphate. PIP\textsubscript{2}: phosphatidylinositol-bisphosphate. PLC: phospholipase C. VEGFR: vascular endothelial growth factor receptor.
Figure 2 Gustatory signal transduction. Sweet, bitter and umami signals are mediated by type II cells. These cells possess G protein coupled receptors and signal through a common intracellular cascade. Receptor stimulation activates gustducin, a taste specific G protein, which stimulates phospholipase Cβ2 (PLC-β2). PLC-β2 hydrolyses phosphatidylinositol-bisphosphate (PIP2) to diacylglycerol (DAG) and inositol-trisphosphate (IP3). This leads to IP3-mediated release of Ca2+ from intracellular stores and Ca2+ influx via opening of Ca2+-channels. The increased intracellular Ca2+ depolarizes the taste receptor cell and stimulates secretion of adenosine triphosphate (ATP) and subsequent ATP-enhanced ATP release. ATP binds to postsynaptic ATP receptors and excites afferent fibers. Concurrently ATP excites adjacent type III cells to release 5-HT, which inhibits ATP release from receptor cells, thereby forming. The released ATP is degraded by NTPDase2, expressed on type I cells. Sour and salty taste may be detected by type III cells via ion-channels by direct entry of H+ and Na+, respectively. This generates a positive inward current and activates voltage-gated Na+-channels. Na+ influx activates voltage-gated Ca2+-channels and subsequent Ca2+ influx leads to exocytosis of neurotransmitters. Both 5-HT and noradrenalin are released from sour and possibly from salty taste receptor cells.
Cell renewal

The average life span of cells within taste buds in rodents is 10 to 14 days with much variation in subsets of cells. For the subset of taste receptor cells, half-life times vary from 8 days for type II cells to 22 days for type III cells. Consistency in taste perception is ensured by the constant renewal of taste receptor cells, in which the Wnt/β-catenin pathway is a crucial factor. Binding of Wnt to its receptor stimulates the intracellular Wnt/β-catenin pathway, which regulates β-catenin levels. Low β-catenin levels promote differentiation of progenitor cells (basal keratinocytes) into differentiated keratinocytes, whereas higher levels promote differentiation into taste cell precursors. These cell precursors express sonic hedgehog, which seems to be the key signal that promotes differentiation into either type I, type II or type III cells in response to high, mid or low β-catenin respectively (Figure 3).

![Figure 3](image)

**Figure 3** Differentiation of progenitors cells into taste cells and non-taste epithelium.

Low β-catenin levels promote differentiation of progenitor cells (basal keratinocytes) into differentiated keratinocytes, whereas higher levels promote differentiation into taste cell precursors. Taste cell precursors express sonic hedgehog (Shh+) and further differentiate into either type I, type II or type III cells in response to high, mid or low β-catenin, respectively.

Physiology of smell
Signal transduction

Olfactory receptor neurons, the receptor cells for smell, are located in the olfactory epithelium. Every receptor neuron is sensitive to a subset of odorants, dependent on the particular receptor molecules they express. There are believed to be about 400 different odorant receptor proteins, which are G protein coupled receptors.\textsuperscript{42} After receptor stimulation, an intracellular cascade is activated. This cascade includes adenylate cyclase, cyclic adenosine monophosphate (cAMP) and Ca\textsuperscript{2+}.\textsuperscript{48,49} The resulting action potential is transmitted via axons, synapsed to mitral cells and projected the brain. The signal transduction route is more extensively described in figure 4.

Cell renewal

Olfactory receptor neurons have a life span of approximately 30-60 days and are constantly replaced by division of basal stem cells. Horizontal cells, a subtype of basal stem cells expressing epidermal growth factor receptor (EGFR), act as a reserve pool after epithelial damage. They are responsive to EGF, a factor shown to be mitogenic for stem cells in the nervous system. The proliferation rate of these cells is increased after injury, so a relatively stable population of olfactory receptor neurons is maintained.\textsuperscript{42,52}

Mechanism of action of protein kinase inhibitors

While most classic cytostatics interact with DNA and as a consequence target all rapidly dividing cells, comprising both malignant and benign cells, PKIs target specific protein kinases.\textsuperscript{2,53} Protein kinases are enzymes that are part of signaling pathways and play a regulatory role in cell proliferation, differentiation and apoptosis, where they catalyze the transfer of phosphate from ATP to the target protein. This changes the shape and function of the target protein and allows it to signal downstream.\textsuperscript{1,3,4} In cancer, protein kinase pathways are dysregulated in several ways. Underlying mechanisms of this dysregulation include protein fusions/mutations resulting in protein kinases which are active in the absence of ligand binding and a decrease in factors that limit protein kinase activation. This aberrant activation and consequent downstream signaling can increase survival, proliferation and migration of cells.\textsuperscript{1,54} The causative role of protein kinases in tumorigenesis makes them important targets for anti-cancer drugs.\textsuperscript{3} These drugs are referred to as small molecule PKIs.
Figure 4 Olfactory signal transduction. Olfactory receptor neurons possess G protein coupled receptors. Receptor stimulation activates adenylate cyclase, a catalyst for the conversion of cytosolic ATP to cyclic adenosine monophosphate (cAMP), and leads to opening of cAMP-gated cation-selective channels. The affinity of these cAMP-gated channels for cAMP is reduced by binding of calmodulin, while phosphorylation of the channel by protein kinase C increases cAMP sensitivity.48 After opening of the cAMP-gated cation channel, Na\(^+\) and Ca\(^{2+}\) influx depolarizes the neuron and opens Ca\(^{2+}\)-gated Cl\(^-\) channels. The resulting Cl\(^-\) efflux eventually results in generation of an action potential. The signal is transmitted to glomeruli in the olfactory bulb and synapsed to mitral cells via glutamate.50 The axons of mitral cells run through the granule cell layer and project to other parts of the brain.\[^{42,51}\] Olfactory signaling is inhibited by GABAergic and dopaminergic input at the level of the glomerulus \[^{42,50}\] and granule cell layer. Olfactory signaling is terminated by Ca\(^{2+}\)/calmodulin kinase II, which is activated by the Ca\(^{2+}\) increase in the olfactory receptor neuron. This kinase phosphorylates adenylate cyclase and inhibits its activity.49
PKIs target the ATP binding site on the kinase, preventing phosphorylation of the kinase and thereby inhibiting protein kinase activity.\textsuperscript{54} This in turn blocks the downstream pathway and thus the malignant signal. Although originally assumed to comprise a targeted only approach, numerous closely interconnected pathways are involved obscuring the complete understanding of the underlying mechanism.\textsuperscript{2} The inhibition of kinases other than the primary target reflects the relatively low selectivity and may cause off-target toxicity by kinase inhibition in normal tissues.\textsuperscript{16,53}

**Potential causes of PKI induced patient-reported taste alterations**

Based on the physiology of flavor perception and the mechanism of action, there are several hypotheses that might explain the development of patient-reported taste alterations. These include taste alteration, smell alteration and neurodegeneration. These hypotheses are described below and shown in figure 1.

*Taste alterations due to oral toxicity*

Oral toxicity, such as oral mucositis and xerostomia (dry mouth), occurs frequently\textsuperscript{14} and is likely to play an important role in taste alterations. Oral mucositis may be related to taste alterations in several ways. Taste alterations could be the introductory demonstration of off-target effects on the oral mucosa, which could later be clinically apparent by the development of oral mucositis. Therefore, the same reasons that have been implicated in the development of oral mucositis could mechanistically explain the initial symptom of taste alteration. Oral mucositis will damage the epithelial cell membranes and may also cause formation of compounds causing off-flavor taste perceptions.\textsuperscript{55} Nonetheless, patient-reported taste alterations during PKIs may be present in the absence of clinical lesions\textsuperscript{14,56}, implying that oral mucositis is not the (only) causal factor. Another oral toxicity that probably contributes to taste alterations includes xerostomia, since this hampers the solubilizing of food particles and therefore a decreased presentation of tastants to the taste receptors.\textsuperscript{5} Further oral factors that may play a role in the development of taste alterations include local disturbance of the immune environment with upregulation of proinflammatory factors and changes in physiologic oral microbiota. These factors have previously been correlated with the development of oral toxicity in the case of other targeted agents, namely mTOR inhibitors.\textsuperscript{57-59}
**Taste alterations by affecting taste receptor cells**

Taste alterations may be caused by distortion of signal transmission of one or more of the five taste qualities. As described above, sweet, bitter and umami taste signal through a common pathway, with secondary messengers including PLC-β2 and IP₃. PKIs interfering with this pathway would be expected to cause taste changes limited to these taste qualities, leaving sour and salty taste as well as smell unaffected. Phosphatidylinositol-bisphosphate (PIP₂) is a second messenger within this pathway. PIP₂ is also a substrate in downstream signaling of pathways activated by receptor tyrosine kinases. Inhibiting these pathways may result in higher intracellular availability of PIP₂. This could be the case for EGFR inhibitors like gefitinib and erlotinib, since a downstream messenger of EGFR is PLC-γ, which hydrolyses PIP₂ into diacylglycerol (DAG) and IP₃. Decreased hydrolyzing of PIP₂ would lead to higher availability. Another downstream pathway of EGFR is the phosphoinositide 3-kinase (PI3K) pathway, in which PIP₂ is also a second messenger. EGFR inhibition of the PI3K pathway may result in less phosphorylation of PIP₂ and thereby to higher levels of PIP₂. Higher levels of PIP₂ could result in increased signal transduction/lower thresholds for specifically sweet, bitter and umami taste.

PKIs may also affect taste as a result of a direct stimulatory effect on the taste receptor. In chemotherapy, this has been proposed as a potential mechanism, either by secretion of the drug into the saliva or diffusion from capillaries. This type of taste alteration has been described as a metallic, ‘chemical’ or bitter sensation during chemotherapy. Because most PKIs are continuously administered, this would probably cause a continuous chemical drug taste from start of treatment until discontinuation. After drug clearance, taste or smell abnormalities may persist due to damage to the receptor cells or to the afferent neuronal cells. This forms a vicious circle with cancer anorexia that leads to decreased food intake which in turn has been correlated with an increased risk of oral toxicity. Furthermore, PKIs may specifically impair the function of the taste receptors for sweet, bitter and umami, via direct effect on the signaling G protein, gustducin. This protein shows structural and functional similarity to transducin, a G protein crucial for the sense of sight. Treatment with targeted agents is often accompanied by ocular toxicities, hinting at the alikeness of the underlying pathobiology.

Another hypothesis to explain PKI induced taste alterations is by affected renewal of taste receptor cells. Differentiation of progenitor cells into specific receptor cells mainly depends on β-catenin levels. β-catenin dynamics may be influenced by several PKIs. For instance, inhibition of fms-like tyrosine kinase receptor-3 (FLT3) prevents dissociation of β-catenin from its complex with E-cadherin, thereby reducing β-catenin signaling. FLT3 inhibitor imatinib has been shown to reduce Wnt-β-catenin signaling and this could also be the case for
other FLT3 inhibitors, like sorafenib and sunitinib. Reduced β-catenin signaling may also be caused by PKIs targeting EGFR, fibroblast growth factor receptor (FGFR) and VEGFR. The downstream pathway of these receptors includes the PI3K-AKT pathway, which has a stimulatory effect on β-catenin. Therefore, inhibition of these receptors, for instance by sunitinib, sorafenib or imatinib, may inhibit β-catenin and influence taste cell renewal. Lower β-catenin levels may lead to less differentiation of progenitor cells into taste cell precursors and/or differentiation into other proportions of type I, II and III taste cells. In case of less differentiation into taste cells, all five taste qualities would be affected, while in case of other proportions of the cell types, sweet, bitter and umami (type II cells) would be more affected that sour and salty taste (type III cells), because for differentiation into type II cells higher levels of β-catenin are needed.

Decreased renewal of receptor cells may also be caused by PKIs targeting sonic hedgehog. Sonic hedgehog is expressed by taste cell precursors and plays a role in normal taste cell renewal. Vismodegib inhibits tumor cell proliferation by targeting the sonic hedgehog-pathway. Blockade of this pathway could also inhibit differentiation of taste cell precursors into taste cells and hereby cause taste loss of all five taste qualities.

Smell alteration by affecting olfactory receptor neurons

Patient-reported taste alterations may also be a result of smell alteration. Olfactory signal transduction is mediated by protein kinase C. This kinase phosphorylates the cAMP-gated cation-selective channel, increasing its cAMP sensitivity and stimulating olfactory signal transduction. Protein kinase C may be inhibited by PKIs, as has been shown for imatinib. Hypothetically, inhibition of protein kinase C would result in reduced olfactory transduction and/or higher threshold values, which would be likely to occur shortly after initiation of therapy. Another kinase involved in olfactory signal transduction is Ca²⁺/calmodulin kinase II (CaMKII), an inhibitor of adenylate cyclase involved in termination of olfactory signaling. Inhibition of CaMKII may reduce termination of olfactory signaling, causing a persistent olfactory signal transduction. There are no PKIs primarily targeting CaMKII, although off target effects have been reported, for instance for sunitinib. Next to reduced olfactory signal transduction, smell alteration may be caused by reduced renewal of olfactory receptor neurons. The cells that are believed to be stem cells in olfactory epithelium (horizontal cells) are responsive to EGF. Treatment with EGFR-inhibitors may lead to blockade of downstream signaling and therefore to less differentiation of these stem cells into olfactory receptor neurons. It can be assumed that a
reduced number results in less odorant stimulation of olfactory receptor neurons and therefore to higher smell perception thresholds.

**Neurodegeneration**

In addition to local, mechanistic causes, taste alterations could be explained by a detrimental effect of PKIs on the neurons and the signal transduction. In vivo data have already demonstrated the degenerative effect of sunitinib on neurons, where impaired VEGFR2 signaling was shown to contribute to increased apoptotic cell death and subsequent neurodegeneration.\(^7^6\) Abnormal neuronal activity may result in specific taste sensation independent of taste receptor stimulation.\(^5\,^6\,^5^5\) Furthermore, the primary somatic sensory cortex, collecting sensory information from taste buds, is located in the parietal lobe. The reversible posterior leukoencephalopathy syndrome has been reported with some PKIs and it usually affects parietal/occipital lobe.\(^7^7\) By extrapolation, one could assume that PKI treatment could perhaps result in a more generalized neuronal disturbance directly at the cortex level, ultimately affecting taste perception.

**Discussion**

Patient-reported taste alterations are a common side effect of treatment with PKIs. To our knowledge, it has never been established whether an objective taste dysfunction develops during PKI treatment, or whether these patient-reported symptoms could have an alternative explanation, for example as a consequence of smell alterations. Fact remains that taste alterations constitute an underrecognized and understudied side effect. Especially in the context of chronic drug administration, taste alterations may result in significant morbidity, as they are associated with weight loss and impaired quality of life, all potentially compromising treatment adherence. However, unclarity on the underlying pathobiology hampers the search for identifying potential treatment options.

We here described the physiology of taste and smell and the mechanism of action of PKIs, ultimately proposing potential explanations of PKI induced patient-reported taste alterations. The potential explanations described here would lead to specific objective changes. It is important to further explore whether patient-reported taste alterations are caused by objective changes in taste, smell, both or also by other factors. Future studies should describe patient-reported taste alterations more detailed and also assess taste and smell function objectively, in
order to provide a better understanding of the underlying pathobiology. This may help to develop treatment options in order to prevent or overcome these symptoms.

Abbreviations

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