Cytokines in Vitiligo

Subjects: Dermatology

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Vitiligo is a chronic autoimmune dermatosis of which the pathogenesis remains scarcely known. A wide variety of clinical studies have been proposed to investigate the immune mediators which have shown the most recurrency.

vitiligo interleukins biologics biological drugs oxidative stress autoimmune diseases

1. Introduction

Vitiligo is a common chronic autoimmune dermatosis, mainly characterized by milky white patches with distinct edges, affecting 1% of the population worldwide [1]. Two clinical forms may be recognized, segmental and non-segmental vitiligo, with the unilateral distribution of the patches and an earlier onset in the segmental variant and a scattered distribution in the non-segmental form [1]. Both clinical manifestations are considered as a continuous spectrum with the same pathologic process, although segmental vitiligo responds to the theory of cutaneous mosaicism [2], which means that two separate cell lines coexist side by side in the skin in the same patient. The most common variant is non-segmental vitiligo, which is characterized by white macules/patches scattered over the body, in particular skin folds and areas around the mucosae (mouth, orbits, genitals, anus, wrists, fingertips), progressing in time in the extent and number of patches, with a symmetrical distribution. White patches usually appear in visible areas which are difficult to cover; for this reason, vitiligo affects the quality of life of patients [3]. The appearance of vitiligo is often associated with autoimmune diseases, such as Hashimoto's thyroiditis [4]; in fact, both high levels of CD8+ cytotoxic lymphocytes in lesions and autoantibodies have been found [5]. Over time, a great variety of factors, such as inflammatory products, reactive oxygen species, trauma, sunlight exposure and genetic factors, may play a significant role in vitiligo, and therefore might be considered potential targets for future and present therapies.

2. Vitiligo Treatment Options: Past, Present and Future Therapies

2.1. Systemic Therapeutic Approaches and Biologics for the Treatment of Vitiligo: Rationale, Efficacy and Safety

As described so far, a great variety of factors is involved in the pathogenesis of vitiligo. Several attempts have been made by the scientific community to find an effective treatment and one of the therapeutic approaches is mainly

based on the use of pro-inflammatory cytokines as targets. In this context, monoclonal antibodies have been synthesized, either derived from human immortalized cells or from other animals, targeting the key factors involved in the physiopathology of different diseases, including vitiligo [6]. For instance, several biologics have been used in order to achieve repigmentation or halt the depigmentation processes. Ustekinumab, a monoclonal antibody blocking both IL 12 and IL-23, is one of these molecules. Originally developed for psoriasis [7], this monoclonal antibody has been used in several patients. Since psoriasis is a much more common condition than vitiligo, it has been used in patients affected both by psoriasis and vitiligo. A case report demonstrated that the antagonism of IL-12/23 action led to the resolution of psoriatic plaques, along with a remarkable improvement of the concomitant alopecia and vitiligo in a patient affected by psoriasis, alopecia areata and vitiligo at the same time. Therefore, it has been hypothesized that cases of vitiligo that are resistant to common treatments could benefit from the use of this antibody [8]. Unfortunately, this case report is the only positive result regarding the use of ustekinumab in vitiligo. One nation-wide study, in fact, demonstrated the new onset of white patches in three patients treated with ustekinumab, thus worsening the pre-existing vitiligo in one more patient [9]. In another study, 15 patients developed vitiligous patches after ustekinumab treatment [10] and another case report described a similar reaction [11]. However, the relationship between ustekinum abuse and the appearance of vitiligo patches should be further investigated. Secukinumab is another tested monoclonal antibody (MAB) that may be considered as a suitable candidate for vitiligo treatment. This biological drug targets IL-17A, an interleukin involved in the pathogenesis of vitiligo, psoriasis and psoriatic arthritis. Again, the studies published to date have led to contrasting results. One case report from 2020 revealed that adalimumab, a TNF-alpha inhibitor, failed in treating psoriasis, but this patient also showed an onset of vitiligo lesions over his body. After the switch to secukinumab, an improvement of the psoriatic lesions and the clearance of vitiligo patches were observed [12]. On the other hand, two studies denied this possibility. In a 2020 case report, two patients who failed a previous systemic treatment for psoriasis switched to secukinumab and vitiligo-like patches appeared over their skin; vitiligo was treated as a side effect with topical tacrolimus, stopping the progression of previous patches [13]. The other study was a 2019 clinical trial. Eight patients were enrolled to challenge the efficacy of IL-17 inhibition but unfortunately most patients developed more lesions than when they started (7/8 patients) and the study was interrupted. Although the trial was prematurely interrupted, the hypothesis of the shift towards the Th1 profile of the lymphocytic population and the intermediate step of Th17.1 was imagined to be the crucial pathogenetic event [14]. New-onset vitiligo may occur as paradoxical skin reaction during treatment with TNFα-IL-17 and IL-12/IL23 inhibitors in patients with other inflammatory diseases [9]. A retrospective study showed that new cases of vitiligo were related to infliximab and adalimumab use (72.2%) and to ustekinumab and secukinumab (22.2%) [9]. However, adalimumab was the major trigger of new-onset vitiligo [9]. The maintenance of the biological therapy after the onset of vitiligo led to stable disease or repigmentation in the majority of cases, whereas the use of biological agents in patients with pre-existing vitiligo had an unfavorable outcome, with vitiligo progression in 43.7% of cases and repigmentation in only one out of eighteen patients [9]. The onset of vitiligo during the treatment with adalimumab [12][15][16][17][18][19] and infliximab [20][21][22][23][24][25][26] for other inflammatory diseases has been widely reported in the literature. The occurrence of vitiligo in patients treated with anti-TNFα has limited their use, although they appear hopeful in stopping the progression of the disease. In a group of six patients treated with anti-TNFα, five patients did not develop any new depigmented patches, although repigmentation was not observed [27]. Some authors suggested that anti-TNFα

may be useful to stabilize vitiligo rather than to favor repigmentation [28]. The results are inconclusive about the use of etanercept, another TNFα inhibitor, in patients with vitiligo, and the low number of patients treated with this biological agent does not allow us to give a final opinion. Etanercept led to a mild improvement of vitiligo in two patients who showed strong cytoplasmic staining for TNF-α in the samples obtained from their margin lesions [29] and in a patient affected by both vitiligo and psoriasis [30]. Nevertheless, an open-label pilot study treatment with etanercept in four patients with vitiligo reported neither improvement nor aggravation of the disease [31]. Hence, the authors did not recommend etanercept as a first-line treatment for vitiligo [30]. A more promising therapy seems to be tofacitinib, a Janus kinase (JAK) inhibitor already used in several inflammatory-mediated diseases. Several studies have been proposed, mostly pilot studies, both paired with and without narrow-band UVB therapy (NB-UVB). Scarce results were observed in the improvement of vitiligo lesions with the use of oral tofacitinib alone [32], two case reports also demonstrated a partial and progressive resolution of depigmentation in a patient treated with oral tofacitinib [33][34] and another pilot study with 16 patients using topical tofacitinib showed positive results, especially in darker skin types and younger patients [35] and one more patient treated with increasing doses of oral tofacitinib after failing UVB therapy [36]. Although all these studies have reported positive results regarding this therapy alone (not paired with NB-UVB), not just regarding the progression but also the re-pigmentation of previously affected areas, confounding factors persist, such as previous NB-UVB therapy and the scarcity of numbers, preventing researchers from drawing any conclusion. On the other hand, several studies have evaluated the combination of phototherapy and tofacitinib together. One of these studies suggests that NB-UVB therapy is mandatory for re-pigmentation to let the melanocytes repopulate affected areas, whereas tofacitinib acts as the immune system inhibitor [37]. This consideration was further proposed by another case report that described a male patient which improved both his vitiligo, alopecia areata and psoriasis lesions after oral tofacitinib and UVB therapy in a three-month period [38]. Finally, a retrospective study with a more consistent number of patients affected by vitiligo reported an almost complete re-pigmentation of vitiligo patches (92% patients) following oral tofacitinib and UVB therapy, compared to patients treated solely with UVB therapy (77% re-pigmentation rate) [39]. All these studies can be summarized by the final considerations of the model proposed by Liu et al.: tofacitinib is a safe drug to use, with only mild side effects, such as plasmatic levels of lipids growing or some moderate weight gain. Both the immunosuppressive and repopulating effects derived from tofacitinib require light exposure, especially for re-pigmentation; oral tofacitinib alone might be useful in monotherapy just for maintenance [40]. On the downside of this treatment, the high cost of this therapy and the chance of developing leukopenia and secondary infections might be considered as two important limitations to the use of this therapeutic approach on a large scale. In fact, a topical administration has been mainly considered, for visible areas such as in the face [41], and in children as well [42], with positive results. Recently, ruxolitinib, a JAK1/2 inhibitor, has been proposed for the treatment of vitiligo. Although JAK1/2 inhibition seems to be a better treatment option compared to JAK1/3 inhibition by tofacitinib, the results obtained from a randomized trial [43] showed comparable effects, whereas other case reports [44][45] have confirmed a lack of significant improvement. As mentioned, IL-6 is implicated in the immunopathogenesis of vitiligo, in particular in active disease [46]. Tocilizumab is an anti -interleukin -6 (IL -6) receptor humanized monoclonal antibody, approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis (JIA). Nadesalingam et al. reported the onset of vitiligo, halo naevi and alopecia areata during treatment of JIA with tocilizumab [47]. This effect is the consequence of the blockade of the IL-6 receptor that inhibits the interaction of IL-6 with its receptors,

thus increasing IL-6 levels in serum [47]. Moreover, the increase in IL-6 levels during treatment with tocilizumab may lead to melanocyte damage [47]. In contrast, tocilizumab was used in a patient with seronegative rheumatoid arthritis and the almost complete resolution of simultaneous lesions of vitiligo was observed; nevertheless, the recurrence of depigmentation at the original sites has been noted after the discontinuation of tocilizumab and the treatment has not resolved genital vitiligo [48]. All these possible targets have been summarized recently in a review about biologic-induced vitiligo, showing that we still lack sufficient knowledge to address the reasons why a drug targeting a specific cytokine involved in the pathogenesis of this condition leads to paradoxical results. **Table 1** presents a short summary of the most common attempted treatments.

Table 1. Biological drugs used for the treatment of vitiligo.

	Target	Desired Effect	Real-Life Effect
Ustekinumab [7][8][9][10][11]	IL-12 and -23	Blocking of inflammation and Th17 polarization	Appearance of new vitiligo patches
Secukinumab [12][13][14]	IL-17A	Interrupting inflammation and production of other proinflammatory cytokines	Progression and appearance of new depigmentation areas
Adalimumab [15][16][17][18][19][27][28], infliximab [20][21][22][23][24][25][26][27][28], etanercept [29][30][31]	TNF-alpha	Stopping the progression of inflammation	Contrasting results in the appearance of new patches and the progression of already existing ones
Tildrakizumab	IL-23	Blockage of the inflammatory network	Insufficient studies
Tocilizumab [47]	IL-6 receptor	Stopping the propagation of inflammation	Soluble form of IL-6 might be causative of new manifestations
Tofacitinib [32][33][34][35][36][37][38][39][40][41][42], ruxolitinib [43][44][45]	JAK1-3 and 1-2	Halting inflammation cascade signals	Stopped progression. Might need concomitant UVB for repigmentation

2.2. Perspectives to Explore

So far, biological therapies have been attempted for several skin diseases but in many cases, the first steps of the research have been characterized by many failed attempts and the appearance of vitiligo as a side effect [49].

Although the biological agents discussed so far have brought about some promising results, the scientific community continues to evaluate new therapeutic frontiers, exploiting new therapeutic targets. In this context, other molecular pathways have been studied using in vitro and in vivo experimental approaches. Anti-IFNγ antibodies were administered with intradermal injections around the lesion or through intramuscular injections, but the number of treated patients was very small (four in total), two of which responded with repigmentation if the drug was administered locally and the other two required, for a response, a subsequent intramuscular administration [50]. In

another study, the researchers reported that IFNγ induces the accumulation of melanocyte-specific CTLs in the lesional skin and vitiligo mice treated with anti-IFNγ antibodies for 5 weeks, stopped the depigmentation and reduced the number of melanocyte-specific CTLs [51]. IFNγ activity is mediated by the JAK-STAT pathway, the inhibition of which by biological agents leads to re-pigmentation via the immunosuppression and repopulation of the melanocytic cells. The CXCL10-CXCR3 axis is an IFN-induced pathway, and its neutralization has been investigated in a mouse model [52]. Mice with established depigmentation treated with CXCL10 neutralizing antibodies for eight weeks showed reversal of the disease with repigmentation [52]. The use of these treatments, such as tofacitinib and ruxolitinib, as previously mentioned, produced the most consistently positive results in terms of efficacy and safety. The inducible form of the NO synthase (iNOS) may be considered as a possible target for future therapies since it is regulated by IFN, IL-33 and IL-6 and might play a role in the stress-related cell damage in vitiligo skin. However, to date, no valid study has been focused in this direction, but this target could be exploited after acute phases of the disease, as a maintenance treatment. T_{RM} cells may infiltrate perilesional skin and are able to trigger vitiligo after the cessation of treatment [53]. Indeed, IL-15 is required for the maintenance of T_{RM} cells in the skin [54]. CD122 is a component of a subtype of the IL-15 receptor, which is expressed on memory T cells [53]. An anti-CD122 antibody has been used to target IL-15 receptors; its blockade has reversed the disease in mice with stable vitiligo [53]. A similar experiment has been performed to stop the recruitment of recirculating memory T cells (T_{CM}) in a vitiligo mouse model [55]. Naïve lymphocytes need to express sphingosine-1 phosphate receptor 1 (S1PR1) and to detect its ligand S1P to access the circulatory system. When entering tissues, memory T cells downregulate S1PR1 to prevent recirculation [56]. In a study by Richmond et al. (2019), the inhibition of S1P in mice reversed vitiligo, indicating that T_{CM} cells cooperate with T_{RM} to maintain disease [55]. Other studies regarding T-reg cells have proposed the use of programmed cell death 1 (PD-1) fusion protein as a possible therapeutic option, considering that T-reg cells play a pivotal role in the pathogenesis of vitiligo. The authors of this study demonstrated a >50% area of repigmentation in this murine model up to 8 weeks of treatment after the last injection, comparing it with simvastatin oral administration, which led to a <1 repigmentation response [57]. As stated in another study, in fact, simvastatin may have a rationale in the treatment of vitiligo since hydroxymethylglutaril-coenzyme A (HMG-CoA) inhibition leads to the stopping of IFN production and CD8+ proliferation, but greater numbers are needed in order to propose this treatment as an option for future therapies [58]. Altogether, these studies suggest the need for further clinical trials to achieve enough enrolled patients which can undergo this type of treatment. **Table 2** produces a short resume of future therapeutic perspectives.

Table 2. Possible targets for the treatment of vitiligo, known effects on melanocytes, molecules related to the objectives, scientific rationale.

Molecule	Involvement	Possible target	Rationale
Pd-1	Immunity response and checkpoint function	PD-1, PD-L1	Regulating T-cell activation
IFN-gamma	Inflammation and promotion of autophagy	IFN-gamma soluble, CXCL10-CXCR3	Stopping specific CTLs killing of melanocytes

Molecule	Involvement	Possible target	Rationale
NOS	Production of oxygen radical species	Inducible synthase (iNOS)	Lower levels of oxidative stress
IL-15	Regulates level of IL-17	Soluble form and receptor CD122	Stopping crosstalk between T_{RM} cells and Tcm cells
S1PR1	Transit from tissues to blood vessels of T lymphocytes	S1PR1 (receptor) or S1P (ligand)	Allowing the recirculation of T memory cells and preventing the maintenance of inflammation

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