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REVIEW

Tailored biological treatment for patients with moderate-to-severe psoriasis

Martina Maurelli, Paolo Gisondi and Giampiero Girolomoni

Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy

ABSTRACT

Introduction: Psoriasis is a common, chronic immune-mediated skin disease frequently associated to inflammatory and metabolic comorbidities. About 20–30% of patients are affected by moderate-to-severe psoriasis and require a systemic treatment, which include traditional and biological drugs. The objective of this manuscript is to provide criteria for a personalized biological treatment.

Areas covered: Tailoring a biological treatment for patients with moderate-to-severe psoriasis needs to consider several variables related to the disease, the patient and the treatment. It is important to consider the disease severity and activity, the skin areas involved, the frequency of relapses, itch or other symptoms, and foremost the presence of comorbidities. About the patient, is important to consider age, gender, body weight, the occupation, the impact on the quality of life, the likelihood of adherence, patient expectations, the desire for remission, and the fear of side effects.

Expert opinion: The presence of comorbidities, which may benefit from or contraindicate a given biologic, is the main driver of a tailored therapy. A personalized treatment associates maximum efficacy and minimal risk of side effects. In addition, there is the possibility of modifying disease-course inducing long-term remission and preventing the development of psoriatic arthritis.

PLAIN LANGUAGE SUMMARY

Psoriasis is a chronic inflammatory disease affecting 2–3% of the population worldwide. It is characterized by erythematous and scaling plaques generally localized on the extensor surfaces, such as elbow and knees. In almost one-third of cases, it is diffuse and affecting wide areas of the body surface including the nails and it is significantly interfering with the patients' well-being. Psoriasis is frequently associated to comorbidities including inflammatory and metabolic disorders such as psoriatic arthritis, obesity and diabetes. Pharmacotherapies including monoclonal antibodies specifically targeting different pathogenetic mediators are available for the treatment of moderate-to-severe psoriasis. Several factors including the age, gender, localization of psoriasis, and comorbidities could influence the treatment selection of targeted pharmacotherapies. A personalized treatment associates maximum efficacy and minimal risk of adverse effects.

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Biological treatment; comorbidities; personalized treatment; pharmacogenomics; psoriasis

1. Introduction

Psoriasis is an immune-mediated and chronic cutaneous disease that affects 1–4% of the Western countries' people. Around 20–30% of chronic plaque psoriasis patients are affected by a moderate-to-severe form and require a systemic treatment, which include photochemotherapy, conventional systemic agents (acitretin, cyclosporine, methotrexate, fumarates), targeted biological drugs, and new small molecules [1–4]. Psoriasis is an immune-mediated disease with both genetic and environmental factors playing a relevant role. Most psoriasis susceptibility loci are related to inflammatory and immune gene. Environmental factors include psychological stress, skin trauma, medications, infections, and air pollution [5–7].

Early events in lesion development include the skin recruitment and activation of plasmacytoid dendritic cells, natural killer cells, and macrophages that secrete cytokines (IFN-α, IL-1β, TNF-α) to drive activation of myeloid dendritic cells. These induce the activation and expansion of autoreactive T lymphocytes. Activated dendritic cells produce IL-12 and IL-23, which regulate the differentiation and expansion of T helper lymphocytes (Th1, Th17, Th22), which in turn produce the pathogenetic cytokines, IL-17, TNF, IFN-γ, and IL-22. These cytokines, particularly IL-17 and TNF-α, act on keratinocytes to promote (directly and indirectly) hyperproliferation and further release of chemokines and cytokines, thus amplifying inflammation and increasing epidermal thickness and desquamation, ultimately producing the typical psoriasis plaque [6].

2. Body

2.1. Psoriasis comorbidities

Patients with moderate-to-severe psoriasis have an increased prevalence of systemic disorders. Psoriatic arthritis (PsA), inflammatory bowel diseases (IBD), and uveitis share genetic background and immune mediated pathways with psoriasis. Obesity and cardiometabolic disorders are also more prevalent in patients with psoriasis. In addition, psychiatric diseases

CONTACT Martina Maurelli maurelli.martina@gmail.com Section of Dermatology and Venereology, Department of Medicine, University of Verona, Piazzale A. Stefani 1, 37126 Verona, Italy

Article highlights

- Psoriasis is a chronic and heterogeneous disease associated with inflammatory and metabolic comorbidities.
- There are different classes of biological drugs targeting different pathogenetic mediators available for the treatment of psoriasis.
- A personalized treatment associates maximum efficacy and minimal risk of side effects. In addition, there is the possibility of modifying disease course inducing long-term remission and preventing the development of psoriatic arthritis.
- The presence of comorbidities, which may benefit from or contraindicate a given biologic, is the main driver of a tailored therapy.

(depression, anxiety, suicidal ideation) may have a higher incidence in patients with severe psoriasis.

2.1.1. Psoriatic arthritis

PsA is the major comorbidity associated with psoriasis characterized by the involvement of different musculoskeletal domains. The prevalence of PsA is around one-third of Caucasian patients with psoriasis, ranging between 6% and 42%, and is highest among patients between 30 and 60 years. The majority of patients first develop psoriasis and only later develop PsA by a median of 8 years, although in 15% of cases, PsA and psoriasis occur simultaneously or PsA precedes cutaneous disease. In many cases, PsA is a mild-to-moderate disease with a fluctuating course, but the risk of development of bone erosion with a disabling form of arthritis is high. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recognized different domains of PsA to suggest a more appropriate treatment to reach the lowest disease activity in each domain. These include peripheral arthritis, axial disease, enthesitis, dactylitis, skin disease, and nail disease. Enthesitis can be found in 30–50% of patients and affects generally the plantar fascia and Achilles' tendon, causing pain around patella, iliac crest and epicondyles. Dactylitis is observed in 40–50% of patients, involving asymmetrically particularly the third and fourth toes, but also other toes and hands [8–11].

2.1.2. Inflammatory bowel diseases

Crohn's disease and ulcerative colitis are the most common forms of IBD. Several studies have reported a higher rate of association between psoriasis and IBD, with a prevalence of IBD in psoriatic patients of 0.3–0.4% and of psoriasis in IBD patients of 3–4% [12–14]. Crohn's disease is significantly increased in patients with psoriasis (HR 1.23, 1.03–1.46) [13,14]. Conversely, ulcerative colitis has not at increased risk (HR 1.01, 0.89–1.14) [15].

2.1.3. Obesity and metabolic syndrome

Psoriasis is frequently associated with metabolic disorders including obesity, because of the increased systemic inflammation induced by visceral adipose tissues releasing adipokines [16]. A higher prevalence of obesity in patients with psoriasis has been reported compared to the health population. Neimann et al. showed that the prevalence of obesity in psoriatic patients is 20.7% with and higher adjusted odds of obesity in patients affected by severe psoriasis (OR, 1.79; 95% CI, 1.55–2.05) compared to controls [16,17]. The presence of obesity modifies the clinical management and the therapeutic approach to psoriatic patients. Obesity is a negative predictor of efficacy of systemic treatments, in particular drugs with a fixed dosage. In obese patients, dietary weight loss interventions should be recommended together with medical treatments, and the weight loss appears to be beneficial in obese patients with psoriasis. Patients with psoriasis also manifest higher prevalence of dyslipidemia, hypertension and nonalcoholic fatty liver disease (NAFLD) [16,18].

2.1.4. Cardiovascular disease

Psoriasis patients manifest a higher prevalence of several cardiovascular risk factors, such as metabolic syndrome, obesity, hypertension, dyslipidemia, and type 2 diabetes, and are at higher risk of cardiovascular diseases. Plaque psoriasis is however an independent risk factor for cardiovascular diseases. Indeed, chronic inflammation associated with psoriasis may play an important role in accelerating atherosclerosis, which may explain the increased risk of major cardiovascular events only in patients with severe psoriasis [18,19]. An estimated prevalence of cardiovascular diseases has been found in North American psoriatic patients (14.3%), compared to healthy subjects (11.3%) [20,21].

2.2. Treatments for chronic plaque psoriasis

Treatments of psoriasis are topical, phototherapy, or systemic. Topical therapy alone is indicated in mild forms of psoriasis, and include topical corticosteroids, vitamin D3 analogues, calcipotriol/betamethasone fixed combinations, keratolytics and topical immunomodulators (tacrolimus, pimecrolimus). The major concern with topical therapy is adherence, which reduces quickly. Narrow band ultraviolet light B (NB-UVB) phototherapy is considered a topic treatment. Another problem about the chronic use of topical corticosteroids, in particular for super potent and potent topical corticosteroids, are atrophy, telangiectasia, and striae distensae. In moderate-to-severe psoriasis, the topicals are usually combined with systemic treatments. Systemic treatments for the treatment of moderate-to-severe psoriasis are classified in conventional agents (acitretin, cyclosporine, methotrexate, fumarates, and PUVA) and targeted therapies (biologics and small molecules). Targeted therapies are in general prescribed when conventional treatments are contraindicated, ineffective, and/or not tolerated. Targeted therapy with monoclonal antibodies that inhibit different cytokines (TNF-α, IL-12/23, IL-17, IL-23), thus blocking the inflammatory cascade and epidermal hyperplasia. Table 1 lists drugs currently approved for the treatment of psoriasis and the efficacy of biological drugs as PASI75 and PASI90, representing an improvement of the PASI index of at least 75% and 90%, respectively [9]. Apremilast is an oral small molecule that inhibit phosphodiesterase 4 (PDE4). In the last few years, the expiration of biologic patents of some TNF-α inhibitors, has encouraged some companies to produce biosimilars, with a reduced cost and a same safety and efficacy profile, compared to their originator. The use of biosimilars is

Table 1. Systemic treatments for plaque psoriasis and their efficacy [9].

	Targeted therapies (biologics and small molecules)			
Traditional systemic agents			PASI75	PASI90
Acitretin	TNF-α inhibitors	Infliximab	80% W10	57% W10
Cyclosporine		Etanercept	38–49% W12	11–21% W12
Methotrexate		Adalimumab	71–80% W16	45–52% W16
Dimethylfumarate		Certolizumab-pegol	66–76% W16	36–44% W16
PUVA	IL-12/23 inhibitor	Ustekinumab	66–76% W12	37–51% W12
	IL-17 inhibitors	Secukinumab	76–87% W12	55–60% W12
		Ixekizumab	77–90% W12	60–71% W12
		Brodalumab	83–86% W12	69–70% W12
		Bimekizumab	92–95% W16	85–90% W16
	IL-23 inhibitors	Guselkumab	86% W12	70% W12
		Tildrakizumab	64% W12	34% W12
		Risankizumab	91% W16	75% W16
	PDE4 inhibitor	Apremilast	29–33% W16	8–10% W16

PUVA, psoralen ultraviolet light A phototherapy.
PASI, psoriasis area severity index; PASI75, at least 75% PASI improvement; PASI90, at least 90% PASI improvement.

a valuable pharmacoeconomic strategy to lower health-care costs, leading to a more accessible and earlier therapeutic option.

The effective and approved treatments for PsA include all anti-TNF agents, including golimumab (all PsA domains), anti-IL-17 drugs (secukinumab and ixekizumab for entheseal, peripheral, and axial disease), and anti-IL-23 drugs (guselkumab and risankizumab) for entheseal and peripheral arthritis [9–11]. Infliximab, adalimumab, certolizumab, and ustekinumab are approved also for the treatment of patients with Crohn's disease. Golimumab is approved for ulcerative colitis but not for Crohn's disease. IL-17 inhibitors have been shown to worsen Crohn's disease and new onset disease has been described in patients treated with anti-IL-17 drugs. In contrast, IL-23 inhibitors showed good efficacy and safety profile in Crohn's disease [18]. About the therapeutic approach of obese psoriatic patients, apremilast may reduce body weight, improve glucose metabolism, and enhance metformin activity, and is the only anti-psoriatic drug that might have beneficial effects on obesity. In contrast, TNF-α blockers increase body weight in a fraction of patients. In addition, it is important to considered that efficacy of several biologic therapies might be affected by body weight and dose adjustment necessary to maintain a satisfactory response in these patients. Infliximab and ustekinumab dosage is weight based and thus are suitable to treat obese patients. IL-17 inhibitors are effective in obese but patients similarly to normal weight patients. Risankizumab is highly efficacious in obese patients [16,18]. About the treatment of patients affected with cardiovascular diseases, TNF-α inhibitors are contraindicated in those with congestive heart failure (New York Heart Association functional class III/IV). Ustekinumab has some potential cardioprotective benefit, but more long-term data are needed. Anti-IL-17 are beneficial in these patients, because alterations of IL-17A and related downstream cytokines lead to vascular inflammatory alterations, such as increased reactive oxygen species (ROS) formation, oxidative stress, endothelial dysfunction, arterial hypertension, and premature death. Also, the inhibition of IL-23 may be beneficial, because IL-23 and IL-23 R are increased in atherosclerotic plaques, and higher levels of IL-23 have been found in patients with current symptoms [21]. In psoriatic patients affected by lupus erythematosus, the treatment with IL-23 inhibitors is a valid option, whereas TNF-α inhibitors are better avoided [22]. About the IL-17 inhibitors, it has been reported an aggravation of discoid lupus erythematosus after treatment with secukinumab for psoriasis [23]. In patients with concomitant multiple sclerosis, fumarates, and IL-17 inhibitors, in particular secukinumab, have proven their efficacy without adverse events; on the other hand, TNF-α inhibitors are contraindicated because they are known to induce or worsen demyelinating diseases [24].

Biologics demonstrated a favorable safety profile in clinical trials and in post-marketing surveillance [25]. TNF-α inhibitors are associated with higher risk of infections, such as herpes zoster, worsening of autoimmune diseases, worsening or reactivation of atopic eczema, and risk of selected malignancy, such as lymphoma and skin cancer. IL-17 inhibitors are associated with risk of candidiasis and to a lesser extent neutropenia, IBD, and eczema reactivation. Reactivation or new occurrence of eczema may occur in patients with psoriasis treated with biologics and may significantly impact these patients because treating one disease phenotype may flare or inadequately control the other, and also have an impact on the management of patients, with a significant proportion of affected patients having to switch biologics. A personal history of atopy has been shown to be associated with these flares. Eczema reactivation is not rare with anti-TNF agents, but It has been described also with anti-IL-17 drugs. Emergence of eczema may be favored by overexpression of Th2 cytokines when the IL-17 or Th1 axes are inhibited. Treatment strategies included no treatment, topical corticosteroids, broad-acting systemic agents, and discontinuation or switch of biologic therapy. Unfortunately, eczema can persist even after discontinuation of the culprit biologic [26]. IL-23 inhibitors have a very favorable safety profile with mild infections being the most common adverse events [27]. All biological drugs are associated with a higher risk of infection or reactivation of latent infections such as tuberculosis (particularly TNF-a inhibitors), viral hepatitis and HIV infection, and with a risk of paradoxical reactions, which consist in the new appearance or exacerbation of inflammatory skin or systemic diseases, such as psoriasiform skin reactions in the case of TNF-a inhibitors and eczema in the case of IL-17 inhibitors, and more rarely granulomatous skin lesions, vasculitis, pyoderma

gangrenosum, arthralgias, and arthritis [28]. However, patients are screened for these infections before they start treatment. In the case of patients with latent tuberculosis, other than tuberculosis prophylaxis, the first-line recommended therapy are anti-IL-17 or anti-IL-23 drugs, which carry a lower risk of tuberculosis reactivation compared to TNF-a blockers. Similar considerations may hold for patients with viral hepatitis or HIV infection. Certolizumab is the biological treatment of choice for pregnant women became it does not cross the placenta. Etanercept and adalimumab are approved for pediatric patients aged 4 years or older, whereas ustekinumab and secukinumab for patients aged 6 years or older. Table 2 reports the biologics for moderate-to-severe psoriasis from the perspective of associated diseases and for some special populations.

3. Conclusion

The elements to consider when selecting a psoriasis therapy are based on the characteristics of the disease, patient-related features and the characteristics of the treatment (Table 3). In particular, it is important to consider disease severity throughout an objective disease score, disease activity (e.g. the emergence of new lesions), the skin areas involved, the frequency of relapses, the severity of itch or other symptoms, and foremost the presence of comorbidities. About the patient, is important to consider age, gender and body weight, the occupation, the impact on the quality of life, the likelihood of adherence, the patient expectations, the desire for remission, and the fear of side effects. Efficacy and safety are crucial for an adequate treatment. The efficacy is based on short- and long-term response rates, the sustained long-term efficacy and the flexibility; the safety is based on tolerability issues (e.g. nausea, headache) and the long-term risk/benefit profile. In addition, some biomarkers can predict the treatment outcome, such as high body mass index that predicts poor response and long-term efficacy to biologicals. Previous treatment failures also predict a suboptimal or inferior response to current treatment. In the case of adalimumab, early trough level may predict a therapeutic response to the drug [29–31].

Tailoring the available treatment options according to the disease and careful considerations about comorbidities is needed to ensure the use of a minimal combination of drugs for a maximal therapeutic effect, in order to guide the physicians to an appropriate selection of the treatment. The introduction of biologics, with a broader spectrum of biological targets, offered the possibility of controlling the disease using a single drug, minimizing the need for additional therapies, and select the most suitable treatment for each patient [32,33]. The therapeutic approach of psoriasis requires a careful selection of the suitable drug considering beneficial or harmful effects, especially for comorbidities, in each patient [16].

Despite biological treatments have proved effective and safe, not all patients obtain the expected results in clinical practice, with a short- and long-term suboptimal response and even varying degrees of (sometimes presumed) adverse events. The variability in response may be influenced by genetic factors, polymorphisms of the genes of the pathological environment, metabolism, or mechanism of action of the drug that could influence the effectiveness/toxicity of biologicals, such as the polymorphisms in the human leukocyte antigens (HLA) genes, in genes that encode cytokines, transporters, receptors and associated proteins, and genes linked in the pathogenesis of psoriasis, tailoring treatment to the individual patient. However, data currently available do not allow such a very personalized treatment approach [32,33].

4. Expert opinion

Choosing the best biological treatment for patients with moderate-to-severe psoriasis needs to take into account a number of variables related to the disease, the patient, and the treatment. In general, the primary goal of a treatment is inducing disease remission and maintaining the remission over time. Models to identify the optimal biologic therapy for treatment of patients with psoriasis at the individual level are being developed, to predict the response of specific biologic, leading to long treatment duration without discontinuation. This helps in minimizing the number of failed treatment attempts [34].

Table 2. Biologics for moderate-to-severe psoriasis from the perspective of the comorbidities.

Comorbidities	Preferred biologic(s)
Psoriatic arthritis (synovitis)	1. Adalimumab, etanercept, infliximab, certolizumab, golimumab 2. Secukinumab, ixekizumab, 3. Guselkumab, risankizumab
Psoriatic arthritis (enthesitis and/or axial)	1. Adalimumab, etanercept, infliximab, certolizumab, golimumab 2. Ixekizumab, secukinumab 3. Guselkumab, risankizumab
Crohn's disease	1. Adalimumab, infliximab, certolizumab, ustekinumab 2. Guselkumab, risankizumab, tildrakizumab
Ulcerative colitis	1. Adalimumab, infliximab, certolizumab, ustekinumab 2. Guselkumab, risankizumab, tildrakizumab
Latent tuberculosis	1. Secukinumab, brodalumab, ixekizumab, bimekizumab, guselkumab, tildrakizumab, risankizumab 2. Ustekinumab
Eczema	1. Guselkumab, tildrakizumab, risankizumab 2. Ustekinumab, brodalumab
Pregnancy	1. Certolizumab
Pediatric patients	1. Etanercept, Adalimumab (patients aged 4 years or older) 2. Ustekinumab (patients aged 6 years or older) 3. Secukinumab (patients aged 6 years or older)

Table 3. Parameters to be considered in the choice of treatment of psoriasis.

Disease-related factors	Patient-related factors	Treatment-related factors
Disease severity (objective disease score)	Age, gender, body mass index	Short- and long-term efficacy and response
Active disease (onset of new lesions)	Occupation	Sustained long-term efficacy
Skin areas involved	Treatment history	Safety (long-term risk/benefit)
Frequency of relapses	Impact on quality of life	Tolerability
Pruritus or other symptoms	Likelihood of adherence	Flexibility
Psoriatic arthritis	Patient expectations	Practicability
Cardio-metabolic disorders	Desire for remission	Impact on lifestyle
Other diseases: inflammatory bowel diseases, uveitis	Fear of side effects	Cost-effectiveness
HLA-Cw6	Desire of fatherhood/motherhood	Convenient for the patient

However, there are other important goals to consider including the role of early intervention with effective therapy, including the possibility of modifying disease course inducing long-term remission and the possibility of preventing the development of PsA. The role of pharmacogenomics is still debated.

4.1. Disease modification, early intervention, and prevention of PsA

The early intervention with biologics, including biosimilars, could impact on the psoriasis course in terms of prevention of PsA, or its progression, with a more persistent efficacy and may modify the natural history of psoriasis [29,35]. Acosta Felquer et al. [36] and Gisondi et al. [37] observed that earlier treatment with biologics may delay or reduce the risk of PsA compared to other treatments [38]. In addition, an earlier onset and uncontrolled psoriasis are associated with the greatest risk of cumulative life course impairment. If managed inadequately, long-term consequences can include the developing of serious comorbidities as disease severity progresses, a deterioration in personal and social relationships, the difficulty gaining and retaining paid employment or improving work prospects, a reduced working capability and/or productivity, a limited earning potential, which may lead to behaviors that further aggravate disease (e.g. poor diet/treatment compliance), the psychological distress, and the economic burden. Svedbom et al. demonstrated that systemic therapy at or before enrollment was associated with a lower risk for severe disease at 10 years compared with later initiation of systemic therapy (odds ratio, 0.24; 95% CI, 0.06–0.90) [39,40]. Iversen et al. showed that when biologic intervention occurs at a late stage of the disease, usually 10 years after the initial onset of symptoms, the homing of tissue-resident memory T cells to the skin leading to chronicity of the disease. The STEPIn study demonstrated that early intervention with secukinumab versus narrow-band ultraviolet B phototherapy in subjects with new-onset psoriasis, can modify the long-term natural course of the disease [41]. In addition, secukinumab demonstrated significant improvement in the symptoms associated with pre-PsA in psoriasis patients. After 24 weeks, in patients with pre-PsA (psoriasis and subclinical joint involvement), was reported a significant improvement of skin involvement, patients complained arthralgias and tender and swollen joint counts, and was demonstrated a subclinical inflammation by magnetic resonance imaging [42]. The early intervention with IL-23 inhibitors may induce a sustained and a long-term clinical remission, throughout an inhibitory effect on the resident memory T cells [37]. In conclusion, there may be a different disease modification effect based on the several classes of biologics and will need to be confirmed in future studies.

4.2. Does pharmacogenomics help in selecting the most appropriate drug?

In about 25–50% of cases, reduced response to drugs or adverse reactions may be determined by the presence of genetic variation (mutation, in less than 1% in the population, or polymorphism, in more than 1%) in genes codifying proteins involved in metabolism, bioavailability, or drug effects; in genes codifying proteins representing the therapeutic target of the drug. Among factors determining the inter-individual variability in response to the drugs, the presence and/or the absence of specific single-nucleotide polymorphisms (SNPs) in psoriasis-risk genes plays an important role. The HLA region are part of the major histocompatibility complex (MHC) and help identify exogenous proteins that may trigger an immune response [6]. The HLA system is located within the psoriasis susceptibility (PSORS)1 locus, mapping on chromosome 6p21. HLA-Cw6 is associated with early-onset psoriasis, guttate psoriasis, and arm, leg and trunk involvement; HLA-Cw6+ patients have different profiles of response to biological drugs [4]. Some biomarkers predict effectiveness, safety, and the efficacy of systemic treatments, biomarkers for TNF-inhibitors (CARD14, CDKAL1, IL-1B, IL-12B, IL-17RA loci, lipopolysaccharide-induced phosphorylation of NF-kB in type 2 dendritic cells) and two for ustekinumab (HLA-C*06:02, variation in an IL-1B locus) [43]. HLA-Cw6+ patients appear to have a lower response to TNF-a blockers and a faster response to ustekinumab [39]. However, at the moment, the use of these markers is not supported by enough robust evidence for clinical use without further validation studies.

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ORCID

Martina Maurelli http://orcid.org/0000-0001-7492-8010
Paolo Gisondi http://orcid.org/0000-0002-1777-9001
Giampiero Girolomoni http://orcid.org/0000-0001-8548-0493

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