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Clinical studies with drugs and biologics aimed at slowing or reversing normal aging processes—emerging results and future perspectives

Ricardo P. Garay[1,2]*

[1]Department of Pharmacology and Therapeutics, Craven Center, 91360 Villemoisson-sur-Orge, France
[2]Department of Life Sciences, Centre National de la Recherche Scientifique, 75016 Paris, France

***Correspondence:** Ricardo P. Garay, Department of Pharmacology and Therapeutics, Craven Center, 46bis, rue Galliéni, 91360 Villemoisson-sur-Orge, France. ricardo.garay@orange.fr
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Abstract

Five families of investigational products are in clinical investigation to slow or reverse normal aging processes [longevity candidates, mesenchymal stem cells, senolytics drugs, sirtuin activators, and nicotinamide adenine dinucleotide $(NAD)^+$ precursors]. The longevity candidates, vitamin D and metformin, appear to significantly reduce all-cause mortality and prolong life expectancy. This should be confirmed by interventional studies. The mesenchymal stem cell family is the most advanced in clinical trial development [phase 2b randomized controlled trial (RCT)]. An allogeneic bone marrow stem cell preparation (Lomecel-B) reduced locomotor frailty in older people. The improvement in locomotion was modest. In the future, attempts could be made to improve potency through a precondition or genetic modification of naive bone marrow stem cells. Autologous adipose stem cell-assisted fat grafting increased graft survival, facial volume, and skin quality. The association of the senolytic drugs dasatinib and quercetin was well tolerated, with low brain penetration of dasatinib and undetectable levels of quercetin. The sirtuin-1 activator resveratrol (combined with physical exercise) improved physical function in older adults with physical limitations. The NAD^+ precursor nicotinamide riboside improved physical exercise performance. In conclusion, Lomecel-B is the most advanced agent in clinical trial development for normal aging processes (phase 2b for locomotion frailty), followed by resveratrol and nicotinamide riboside.

Keywords

Aging, clinical trials, frailty, longevity, rejuvenation, senolytics, stem cells, vitamin D

Introduction

Aging is characterized by a slow loss of organ function, reducing vitality, resilience, and healthy life expectancy. The International Conference on Frailty and Sarcopenia Research (ICFSR) clinical practice

guidelines (CPGs) specify that there is no specific medical or biological treatment for these normal conditions of aging. The ICFSR does not recommend any of the non-specific pharmacological treatments currently available (only therapeutic interventions based on exercise and nutritional supplements are recommended) [1].

A substantial effort is currently deployed to find specific drugs and biologics intended to slow or reverse normal aging processes. Currently, several literature reviews are available that identify and analyze clinical studies with the following specific families of compounds (Table 1): (i) longevity candidates [2, 3], (ii) mesenchymal stem cells [4–6], (iii) senolytics drugs [7–9], (iv) sirtuin activators [10–13], and (v) nicotinamide adenine dinucleotide $(NAD)^+$ precursors [14–18].

Table 1. Drugs and biologics that have shown positive results in clinical research to slow or reverse normal aging processes

Family	Indication	Leading agent	Study type	Reference
Longevity candidates	Longevity	Vitamin D	Observational	[34, 36]
		Metformin	Observational	[40]
Mesenchymal stem cells	Locomotion frailty	Lomecel-B	RCT (phase 2)	[47]
	Facial rejuvenation	SVF	RCT	[54]
Senolytics drugs	Cognitive decline	D + Q	OL (phase 1)	[58]
Sirtuin activators	Aging frailty	Resveratrol	RCT (phase 2)	[61]
NAD^+ precursors	Physical performance	NRS	RCT	[65]

SVF: stromal vascular fraction; D + Q: dasatinib and quercetin; NRS: nicotinamide riboside supplements; OL: open-label

An overview of emerging results and future perspectives from clinical studies conducted with the five compound families mentioned above is presented here. Preclinical data and details about ongoing clinical trials (without results) can be found in the literature reviews cited above [2–12, 14, 15]. The reader interested in pharmacological mechanisms and biomarkers can consult the reviews by Nielsen et al. [16], Tchkonia et al. [19], Moskalev et al. [20], and Fraser et al. [21].

Longevity candidates

Twenty years ago, the National Institute on Aging (NIA, USA) launched an Intervention Testing Program (ITP) dedicated to identifying longevity candidates in a genetically heterogeneous mouse model (candidates are evaluated in three independent laboratories) [22]. The ITP has identified two longevity drug candidates, the immunosuppressant rapamycin [23] and the antidiabetic acarbose [24] that are currently under clinical investigation [3]. Vitamin D and the antidiabetic drug metformin have been identified in other animal models and are also under clinical investigation [3, 25].

The mechanism by which these longevity candidates prolong animal lifespan is unclear. Rapamycin is a [mammalian target of rapamycin (mTOR)] kinase inhibitor, which possesses immunosuppressive and antiproliferative properties [25]. Ehninger et al. [26] have suggested that rapamycin extends lifespan in mice by suppressing cancerogenesis. Acarbose is an inhibitor of alpha-glucosidases, a class of intestinal enzymes necessary to digest carbohydrates [27]. Acarbose exerts anti-inflammatory effects on human monocytic THP-1 cells [28], and Sadagurski et al. [29] suggested that acarbose may prolong lifespan in mice by inhibiting age-related hypothalamic inflammation. Metformin appears to exert antiaging actions via multiple mechanisms, including nutrient sensing, DNA repair, oxidative stress, telomere attrition, inflammation, cellular senescence, stem cell decline, and autophagy [30]. Finally, vitamin D is a gene expression modifier (acting on more than 200 genes) and has pleiotropic biological actions [31].

Emerging results with vitamin D

Vitamin D is mainly synthesized in skin exposed to sunlight, and strong sunlight at equatorial latitudes leads to high mean serum concentrations of 25-hydroxy vitamin D [25(OH)D = around 115 nmol/L] [32]. On the contrary, low levels of 25(OH)D (< 50 nmol/L) have been found in a considerable proportion of individuals from temperate countries, 40% in Europe and 24% in the USA [33]. In China, the prevalence of vitamin D deficiency in older adults was 68.4% (in 2014) [34, 35].

A recent observational and Mendelian analysis in middle-aged European persons [36] suggested a causal relationship between low levels of 25(OH)D (< 40 nmol/L) and all-cause mortality. In China, all-cause mortality was significantly higher in subjects with low vitamin D status, and the change from vitamin D deficiency to no deficiency was associated with a lower risk of all-cause mortality [34].

Emerging results with metformin

Kulkarni et al. [37] conducted a phase 4, crossover design RCT (ClinicalTrials.gov identifier: NCT02432287) to investigate the effect of metformin on metabolic and nonmetabolic regulation pathways in skeletal muscle and subcutaneous adipose tissue from 14 older adults (around 70 years old). Participants received oral metformin (1,700 mg/day) or placebo for 6 weeks. Metformin was found to significantly modify gene expression (RNA sequencing) in biopsies from skeletal muscle (647 genes) and subcutaneous adipose tissue (146 genes) [37]. These transcriptomic changes included several well-known anti-aging genes from the GenAge database [37, 38]. In addition, a Mendelian randomization study using UK Biobank data [39] showed that metformin use was associated with younger phenotypic age.

Campbell et al. [40] reviewed observational studies comparing all-cause mortality in patients with diabetes taking metformin with non-diabetics, or with diabetics receiving non-metformin therapies. The results suggested that metformin reduces all-cause mortality independently of its antidiabetic effect [40].

Several clinical trials have been conducted with metformin for aging-related diseases, but they are outside the scope of this article for a recent review, see [41].

Perspectives of clinical research with longevity candidates

All-cause mortality is a marker of longevity [3]. The above results from observational studies suggest that vitamin D supplementation [in persons with low 25(OH)D serum levels] [34, 36] as well as metformin [40] can significantly reduce all-cause mortality and prolong life expectancy (Table 1). This prolongevity efficacy should be confirmed by interventional studies.

A phase 3 clinical trial with metformin [Targeting Aging with Metformin (TAME)] was planned to assess the time to new onset of a composite outcome including cardiovascular events, cancer, dementia, and mortality [42, 43]. TAME plans to include 3,000 participants, aged 65–79 years, at 14 centers across the US. In 2015, TAME started a discussion with the Food and Drug Administration (FDA, USA), but to this day it is not included in the ClinicalTrials.gov database.

According to Barzilai et al. [43], the goal of TAME was to demonstrate "that metformin modulates aging and its diseases, beyond an isolated impact on diabetes". According to Glossmann and Lutz [44]: "The acronym chosen and the intention behind it – namely, that aging is a 'disorder' that can be treated like any other disease – was a clear provocation.".

It is interesting to mention that two other longevity candidates (rapamycin and acarbose) are currently in clinical trials, but the results have not yet been reported to ClinicalTrials.gov [3].

Mesenchymal stem cell preparations

Mesenchymal stem cell preparations and multipotential stromal cells were in development for locomotion frailty and facial skin aging [4].

Positive results on locomotion frailty

Physical frailty in the elderly is characterized by reduced locomotor activity [1], and locomotion frailty is associated with an increased risk of falls, disability, and hospitalization [45].

Lomecel-B (Longeveron, USA) is an allogeneic bone marrow stem cell preparation expanded in culture [46]. The [allogeneiC human mesenchymal stem cells in patients with aging fRAilTy via intravenoUS delivery (CRATUS)] trial [46, 47] included: (i) a phase 1 safety study in 15 frail aging patients followed for 1 month [46], and (ii) a phase 2 RCT [47] investigating the efficacy of intravenous Lomecel-B to reduce physical frailty in 30 elderly subjects with mild to moderate locomotion frailty (treatment period:

6 months). The phase 1 study showed that Lomecel-B was safe and immunologically tolerated [46]. Participants in the phase 2 RCT [47] received 100 million cells (n = 10), 200 million cells (n = 10), or placebo (n = 10). The 6-min walk distance (6-MWD) increased significantly in the 100 m group (from 345.9 m to 410.5 m, mean values at baseline and 6 months, respectively). Immunotolerability was acceptable. Tumor necrosis factor (TNF)-alpha levels decreased significantly.

Lomecel-B is a candidate for further development in phase 3 trials.

Perspectives of clinical research with stem cell preparations for physical frailty

Locomotion frailty improvement with intravenous Lomecel-B was modest [48]. Preconditioning of naive bone marrow stem cells (with growth factors, drugs, or other agents), as well as genetic modification, can improve their therapeutic efficacy [49]. On the other hand, intravenous administration risks trapping the stem cells in the lungs [50]. In such a case, (smaller) exosomes may be an option to increase efficacy.

Several other phase 1 and 2 clinical trials with stem cell preparations are currently underway [4]. In particular, a clinical trial (NCT04314011) using an allogeneic preparation of umbilical cord-derived stem cells was recently completed, but the results have not yet been reported to ClinicalTrials.gov.

The use of allogeneic stem cell preparations may limit its clinical application. Predictive markers of graft rejection are being developed [51], markers that could help identify patients at risk of tissue rejection before administering stem cells.

Positive results on facial skin aging

Facial skin aging is due to natural causes, as well as extrinsic factors (especially sun exposure: photoaging). The [stromal vascular fraction (SVF)] is a preparation of human adipose stem cells obtained by liposuction, followed by collagenase digestion and centrifugation [4, 52, 53]. Yin et al. [54] conducted an RCT to investigate autologous SVF-assisted fat grafting for facial rejuvenation. Fifty patients were randomly assigned into two groups: an intervention group (n = 25) and a control group (n = 25, fat grafting only). SVF-assisted autologous fat grafting increased graft survival, facial volume, and skin quality (Table 1).

Perspectives of clinical research with stem cell preparations for facial rejuvenation

Several clinical trials for facial skin aging are currently underway in Egypt, Indonesia, Cuba, Iran, and Malaysia [4]. Autologous SVF preparations are regulated as biological products by the FDA (USA) because they require mechanical processing [4, 41], and very numerous clinical trials with autologous SVF preparations for facial rejuvenation [53] are not registered on ClinicalTrials.gov. This was not the case with the study of Yin et al. [54], which was registered in ClinicalTrials.gov (NCT02923219) as well as other clinical trials conducted in Egypt (NCT03928444) and Indonesia (NCT05508191) [4]. Results from trials NCT03928444 and NCT05508191 have not yet been posted to ClinicalTrials.gov. The application of similar RCT protocols could pave the way for autologous SVF preparations (in the USA) to be registered on ClinicalTrials.gov and comply with FDA regulations.

Senolytic drugs

Cellular senescence stops the proliferation of damaged or dysfunctional cells [7]. Aging is associated with the accumulation of senescent cells in various tissues and organs. In 2011, the group of Baker et al. [55] showed that killing senescent cells using a transgenic suicide gene is beneficial in preventing or delaying tissue dysfunction and prolonging lifespan in mouse models. Subsequently, the same group reported the discovery of senolytic agents in animal models: (i) the combination of D + Q in 2015 [56], and (ii) fisetin in 2017 [57].

Results

Gonzales et al. [58] recently reported the results of a 12 week, phase 1 clinical trial investigating the safety and cerebrospinal fluid (CSF) penetrance of D + Q in 5 participants (aged 70 years to 82 years) with early-stage symptomatic Alzheimer's disease (Table 1). D + Q (100 mg and 1,000 mg respectively) were orally

given for two days, followed by a treatment interruption of 13 days to 15 days, for a total of 6 cycles. Treatment was well tolerated and was not discontinued prematurely [58]. Low levels of dasatinib were detected in the CSF of 4 participants. Quercetin was not detectable in the CSF.

Perspectives

Several senolytics, including D + Q and fisetin, are in development for cognitive decline [59], aging frailty, and skeletal health in normal postmenopausal women [7]. A clear advantage of some senolytics (quercetin, fisetin) is that they are natural products [60], but it seems too early to draw conclusions about clinical research with senolytic agents.

Sirtuin activators

Human sirtuins are a family of 7 signaling NAD^+-dependent protein deacetylases that are involved in metabolic regulation, resistance to stress, and cellular processes, including aging and cell death [10, 11]. The natural polyphenol resveratrol is a powerful activator of sirtuin-1 (SIRT1) [12, 13]. Curcumin (another natural polyphenol) is a non-specific activator/upregulator of sirtuins (mainly influencing SIRT1 and SIRT3) [13].

Positive results

Harper et al. [61] have recently conducted a pilot clinical trial showing that resveratrol and exercise combined improve aging frailty (Table 1).

Perspectives

The positive results of the pilot trial by Harper et al. [61] deserve confirmation in larger-scale trials.

NAD^+ precursors

A large body of evidence clearly shows that aging is associated with a reduction in cellular NAD^+ levels [14–18]. In particular, Mouchiroud et al. [62] found that NAD^+ levels are reduced in aged worms (the nematode *Caenorhabditis elegans*) and aged mice and that decreasing NAD^+ levels reduced worm lifespan. Zhu et al. [63] reported a decrease in intracellular NAD^+ levels in the healthy aged human brain *in vivo*. Massudi et al. [64] found a strong negative correlation between age and NAD^+ levels in human pelvic skin samples.

Barker et al. [14] published a systematic review of 26 trials that investigated the effect of NAD^+ precursors on physical frailty outcomes. Only four of these trials enrolled participants with a mean age of 60 years or more [14]. Of these, only two trials included healthy participants. Dolopikou et al. [65] found that NRS significantly improved exercise performance (isometric peak torque and fatigue index) in the elderly. Martens et al. [66] reported that NRS elevates NAD^+ levels in circulating peripheral blood mononuclear cells of healthy middle-aged and older adults.

Concluding remarks

Clinical research with drugs and biologics intended to slow or reverse normal aging processes has only recently begun [2–18]. Positive results are beginning to emerge from the very numerous clinical trials (and observational studies) launched worldwide (Table 1).

Research highlights and perspectives:

(1) Vitamin D and metformin are leaders in the clinical development of longevity candidates (Table 1). Observational studies strongly suggested that these compounds can significantly reduce all-cause mortality (and prolong life expectancy) (Table 1). This prolongevity efficacy should be confirmed by interventional studies.

(2) Intravenous Lomecel-B (a mesenchymal stem cell preparation) showed efficacy in reducing locomotor frailty in older people. However, the frailty improvement was modest. Preconditioning

and/or genetic modification of naive mesenchymal stem cells can improve their therapeutic efficacy. The use of allogeneic stem cell preparations may limit its clinical application. Predictive markers of graft rejection are being developed, markers that could help identify patients at risk of tissue rejection before administering stem cells.

(3) An RCT on facial rejuvenation [54] was registered on ClinicalTrials.gov (NCT02923219) and showed that an autologous fat graft enriched with human adipose tissue stem cells improves graft survival, facial volume, and skin quality. The application of a similar RCT protocol could pave the way for autologous SVF preparations to be registered on ClinicalTrials.gov and comply with FDA regulations.

(4) Senolytic drugs (including D + Q and fisetin), the SIRT1 activator resveratrol, and the NAD^+ precursor nicotinamide riboside (NR) are being developed to slow normal aging processes, but it seems too early to draw conclusions about the current clinical research with these compounds.

Abbreviations

25(OH)D: 25-hydroxy vitamin D

CSF: cerebrospinal fluid

D + Q: dasatinib and quercetin

FDA: Food and Drug Administration

NAD: nicotinamide adenine dinucleotide

NRS: nicotinamide riboside supplements

RCT: randomized controlled trial

SIRT1: sirtuin-1

SVF: stromal vascular fraction

TAME: Targeting Aging with Metformin

Declarations

Author contributions

RPG: Conceptualization, Writing—review & editing.

Conflicts of interest

The author declares that he has no conflicts of interest.

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Consent to participate

Not applicable.

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