Concise Review

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STANDARDS, PROTOCOLS, POLICIES, AND REGULATIONS FOR CELL-BASED THERAPIES

Concise Review: A Safety Assessment of Adipose-Derived Cell Therapy in Clinical Trials: A Systematic Review of Reported Adverse Events

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Key Words. Adipose-derived stromal cells • Stromal vascular fraction • Safety • Adverse events • Complications

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ABSTRACT

The popularity of adipose-derived cell therapy has increased over the last decade, and the number of studies published annually is growing. However, concerns regarding safety in the setting of previous malignancy or the use of allogeneic cells have been raised. We therefore aimed to systematically review all clinical studies using adipose-derived cell therapy to identify reported adverse events with a special focus on risk of thromboembolic, immunological, and oncological safety concerns. Our systematic search resulted in 70 included studies involving more than 1,400 patients that were treated with adipose-derived cell therapy. Safety assessment method was not described in 32 of the included studies. For studies involving systemic or cardiac administration, one case of pulmonary thromboembolism and cases of both myocardial and cerebral infarctions were described. In the setting of allogeneic cell therapy studies, where the production of specific antibodies toward donor cells was examined, it was noted that 19%–34% of patients develop antibodies, but the consequence of this is unknown. With regard to oncological safety, only one case of breast cancer recurrence was identified out of 121 patients. Adipose-derived cell therapy has so far shown a favorable safety profile, but safety assessment description has, in general, been of poor quality, and only adverse events that are looked for will be found. We encourage future studies to maintain a strong focus on the safety profile of cell therapy, so its safeness can be confirmed.
STEM CELLS TRANSLATIONAL MEDICINE *2017;6:1786–1794*

SIGNIFICANCE STATEMENT

This study reviewed the safety of adipose-derived cell therapy. Thromboembolic complications were noted following systemic administration of cells. The treatment has so far shown to be safe in the setting of previous cancer. Donor-specific antibodies are produced when using allogeneic cells, documenting that these cells are not immune privileged. The consequences of this needs further research. Future research should focus on higher quality of reporting of adverse events, as the present literature is of low quality.

INTRODUCTION

The field of regenerative medicine has been rapidly expanding over the last decade and especially cells derived from adipose tissue have received a lot of attention due to the ease of harvest and obtainable number of cells [1, 2]. The cells from adipose tissue can be used for therapeutic purposes, either freshly isolated as the stromal vascular fraction (SVF, also called adipose-derived regenerative cells [ADRC]), or culture-expanded as the adipose-derived stem cells (ASC). Adipose-derived cell therapy has shown potential in almost every preclinical animal model [3–7] and the time is ripe for clinical translation of this potential.

The first results published from a clinical trial using adipose-derived cell therapy, published in 2005, were for the treatment of Crohn's fistula [8]. Since then, a steady increase of publications and in treated conditions has occurred. However, as of yet there is still no clear evidence for the implementation of adipose-derived cell therapy in the daily clinical routine.

The mechanisms of action of adipose-derived cell therapy have been hypothesized to be through different pathways, such as paracrine secretion of growth factors, cytokines and microRNA promoting angiogenesis and modulating the immune response, as well as the ability of cells to differentiate into a variety of different cell types. However, very rarely can a beneficial effect be expected without the risk of adverse events. Consequently, safety concerns have been raised

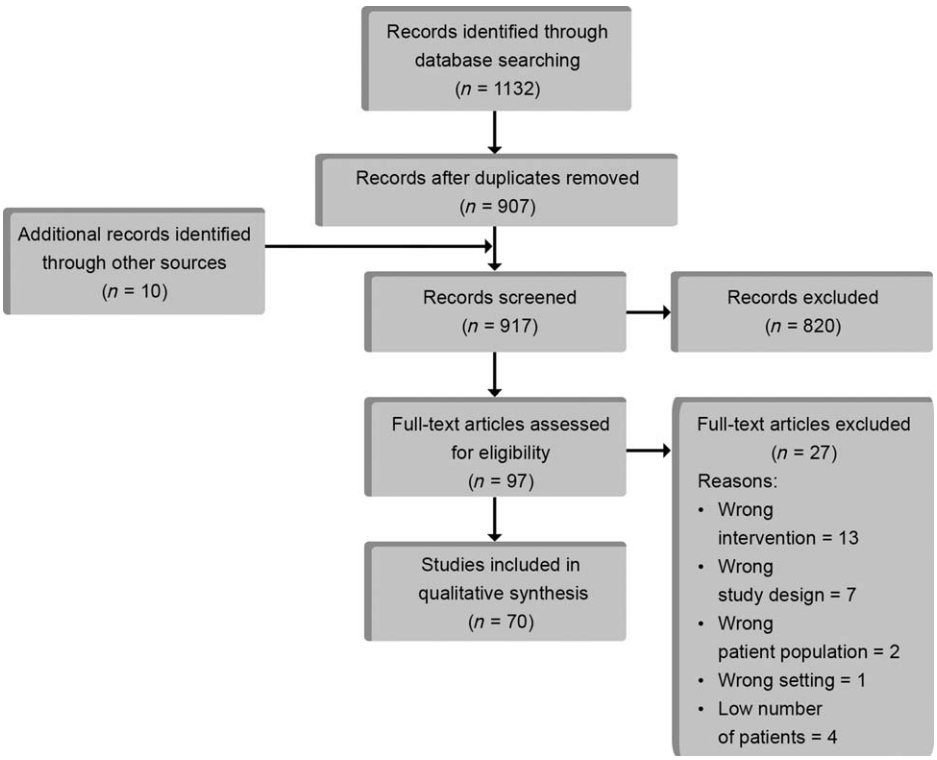


Figure 1. Flow chart of article selection process.

regarding the use of systemically administered cell therapy due to risk of thromboembolic complications [9, 10], the use of allogeneic cells and possible rejection [11], and in the setting of previous cancer therapy [12–14].

The aim of this systematic review was therefore to collect and review all reported adverse events related to adipose-derived cell therapy with a focus on thromboembolic, immunological, and oncological safety concerns.

Materials and Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [15]. A systematic search was performed on PubMed using the following search string: "([adipose stem cell] OR [adipose stromal cell] or [adipose regenerative cell] or [stromal vascular fraction] or [processed lipoaspirate]) AND (trial or trials or pilot or 'feasibility study' or 'safety study')." A similar search was performed on EMBASE. All search results were imported to Covidence for further evaluation [16]. Study selection was performed by two independent assessors (NMT and & MGJ). First, all studies were screened based on title and abstract. Secondly, full text versions of included studies were read for further evaluation. A hand search was also performed by skimming the references of included studies.

Inclusion criteria were human studies using adipose-derived cells for treatment of any given disease published no later than 31st of December 2016. Exclusion criteria were non-English language, reviews, case reports, or case series with fewer than five patients and animal or in vitro studies.

Data retrieved from included studies were year of publication, country of origin, disease treated, study design (randomized controlled trial, nonrandomized study, or case series/pilot study), primary aim (safety or efficacy), cell type used (freshly isolated or culture-expanded as well as autologous or allogeneic), cell dosage, cell characterization (cell count/viability, surface marker analysis, and fibroblastoid colony forming units assay [CFU-F]), number of participants, safety reporting described clearly in the Methods section (yes/no), and the reported adverse events including all-cause mortality. The primary aim was set to safety if this was explicitly stated or was mentioned with equal weight as efficacy. The safety reporting was set to "yes" if anything pertaining to the evaluation of adverse events was noted in the Methods section, and it was set to "no" if nothing at all was described.

All studies with a comparison group were also evaluated for risk of bias using the Cochrane Collaboration tool where safety was set as outcome measure [17]. In brief, seven aspects are evaluated for risk of bias and given an evaluation of either low risk, unclear, or high risk of bias. The seven aspects are random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other areas of bias.

Results

Description of Included Studies

In total, 907 unique studies were identified using our search string. In addition, 10 studies were found through hand search. After screening title and abstract, 97 studies remained. Full text evaluation excluded a further 27 studies leaving 70 studies to be included in the review with a total of 1,474 patients treated with adipose-derived cell therapy (Fig. 1). Almost all organ system have been implicated in adipose-derived cell therapy. The indication for treatment in the included studies was (in order count) soft tissue

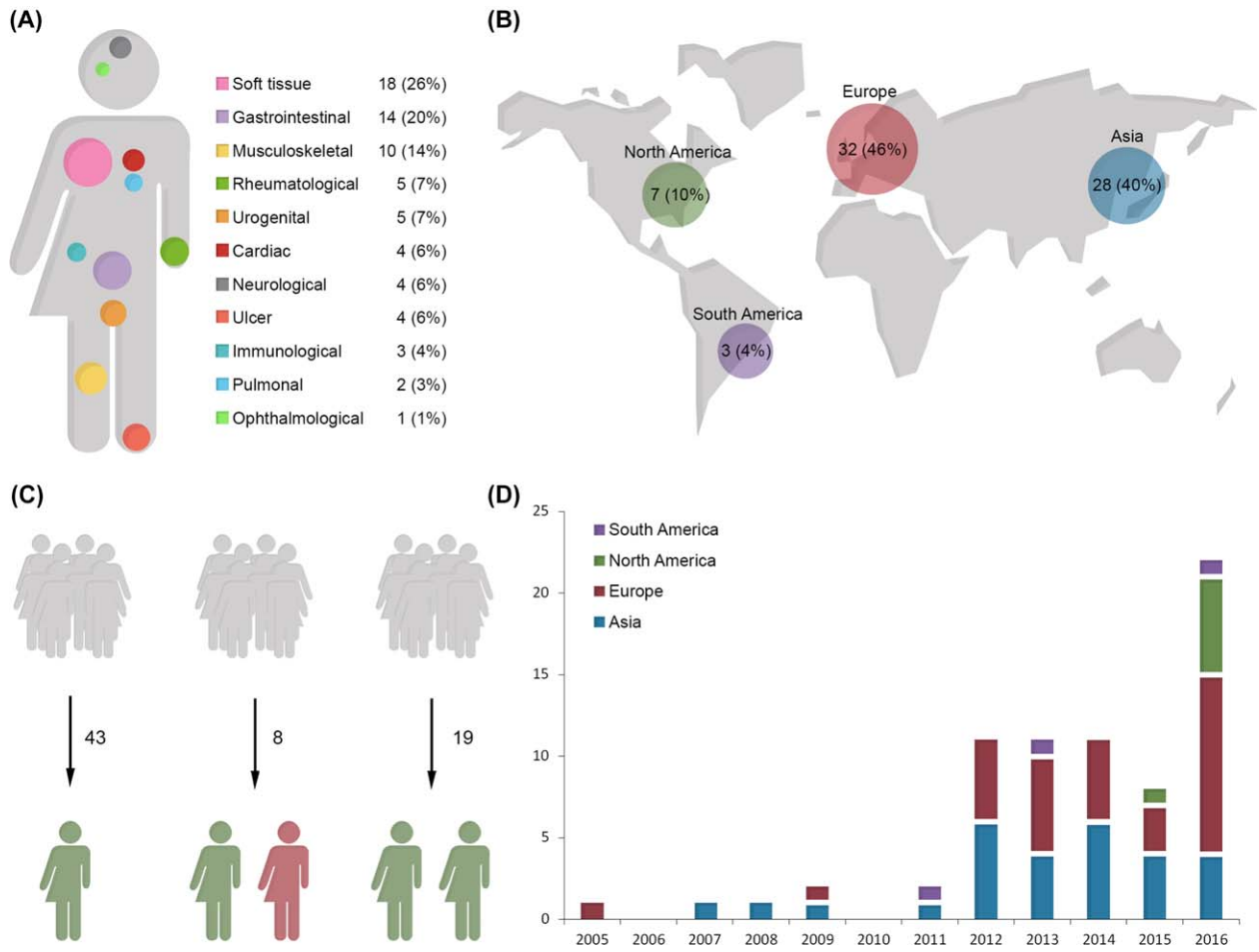


Figure 2. An overview of included studies. **(A):** Graphical overview of the range of indications adipose-derived cell therapy has been used for. **(B):** Graphical overview of research activity bias on geographic location showing that the majority of included studies are from either Europe or Asia. **(C):** The majority of studies were of case series quality with no control group for comparison. Eight of studies included a nonrandom control group and 19 studies were randomized studies. **(D):** Since the first publication in 2005 there has been a steady rise in research output of clinical studies using adipose-derived cell therapy.

[18–35], gastrointestinal [8, 36–48], musculoskeletal [49–58], rheumatological [59–63], ulcer/ischemic limb [64–67], urogenital [68–72], cardiac [73–76], neurological [77–80], immunological [81–83], pulmonary [84, 85], and ophthalmological [86] (Fig. 2A). Studies were performed worldwide but Europe and Asia have so far published the majority of studies using adipose-derived cell therapy (Fig. 2B).

The majority of studies [43] were small in scale and conducted as a series of cases without a comparison group. There were eight studies comparing adipose-derived cell therapy with a nonrandom control group, and 19 studies were conducted as randomized controlled trials (Fig. 2C). The first clinical study using adipose-derived cell therapy was published in 2005. Since then, a steady rise in publications has followed with an explosive growth annually since 2012 (Fig. 2D).

Overview

In the included studies ADRC treatment was given in 36 studies, whereas ASC was used in the 32 studies (two studies included both ADRC and ASC). The most frequent method to characterize cells was cell count with viability estimation. Cell dosage was not specified in fourteen studies in which the indication was soft tissue reconstruction [20, 22, 23, 25, 26, 28, 29, 31, 32], gastrointestinal [47], musculoskeletal [49], neurological [80], or urogenital disease [71, 72]. In addition, 38 studies performed surface marker analysis of cells or at least had set release criteria for certain surface markers in studies using ASCs. CFU-F was performed in only ten studies.

Almost any cell administration pathway was represented in the included studies. Remarkably, a total of 32 of 70 studies did not clearly describe any form of adverse event evaluation in the Methods section, including four studies in which safety was designated as the primary outcome [8, 50, 52, 73] (Supporting Information Table S1). The severity of adverse events depended on the underlying condition being treated, but no studies identified any adverse event as being related to the adipose-derived cell therapy.

Thromboembolic Safety and Mortality

For studies administering cells systemically or intramyocardially, possible thromboembolic complications and all-cause mortality were evaluated. Three RCT studies and one case series administered cells for cardiac indications with various methods.

Two double-blinded RCT trials that were published together administered autologous ADRC intramyocardially with the difference between the two studies being cell dosage (40 or 80 $\times$ 10^6 cells vs. placebo) [76]. Enrollment was terminated prematurely due to adverse events. In total, 31 patients were included and 17 received ADRC. Two patients treated with ADRC experienced cardiac death on day 2 and 291 after administration, and one experienced myocardial infarction at an unknown time point. In addition, a cerebrovascular event occurred in two patients in the ADRC group and one in the placebo group within 24 hours of injection. All neurological symptoms had complete or near-complete recovery. The RCT study by Houtgraaf et al. administered ADRC intracoronarily for myocardial infarction with no mention of specific thromboembolic complications or deaths [74].

In an RCT study by Perin et al., who administered ADRC transendocardially, one out of 21 patients developed myocardial infarction immediately following injection and died [75]. One patient out of six died in the control group. In a case series by Comella et al., which used a similar administration method for ADRC in 28 patients with chronic ischemic cardiomyopathy, three patients died after 1, 7, and 12 months [73].

Three RCT studies and two case series administered cells intravenously for various indications. One dose-escalating RCT study by Álvaro-Gracia et al., administered allogeneic ASC intravenously for the treatment of rheumatoid arthritis and observed a case of lacunar infarction in the low-dose treatment group, eight days after cell administration [61]. No further thromboembolic events occurred.

Vanikar et al. conducted a three-armed randomized trial administering ASC together with hematopoietic stem cells versus hematopoietic stem cells alone versus no cell treatment to minimize rejection following renal transplantation [82]. Herein the distribution of cardiovascular deaths was not significantly different across the groups of which 6/95 treated with ASCs died of either cardiovascular or cerebrovascular events compared with 9/190 in the two other groups combined. The all-cause mortality in patients treated with ASCs was 7/95 compared with 20/190, which was not statistically significant. The remaining RCT and case series administering cells systemically or using near-systemic administration did not describe cases of thromboembolic events [81, 83, 84]. See Table 1 for overview of reported complications.

The evaluation of thromboembolic complications and mortality included two subgroups of studies that used either autologous ADRC for cardiac indications, administered within the heart, or allogeneic ASC, administered intravenously for a variety of indications. It can be difficult to assess the mortality rate in studies without a control group, especially considering that the patient categories included were of poor prognosis to begin with. For the studies including controls there was no indication of an increased mortality for patients receiving cell therapy.

Thromboembolic complications were few, and the comparison across studies was difficult due to heterogeneous cell administration, as three different administration routes were applied in the four cardiac studies. It must also be taken into account that the complications noted were not necessarily due to the cell treatment, as the time frame between cell treatment and complications was not always clearly described.

Immunological Safety

Possible immunologic complications were noted for studies administering allogeneic cells (Table 1). This included four RCTs and seven case series.

Two RCTs evaluated the production of donor-specific antibodies as a measure of immune reaction. In the study of Panés et al., 34% of patients without prior IgG HLA class I antibodies generated anti-HLA class I antibodies during the study period [44]. There were, however, no noted immune reactions or adverse events associated with the donor-specific antibodies, and the presence of the antibodies was not associated with the therapeutic response. In another study using similar allogeneic ASC for intravenous administration, it was noted that 19% of patients developed donor-specific antibodies [61]. The most frequent adverse event was transient fever following cell administration (9/46 treated patients).

The remaining two RCTs did not evaluate the immune response to allogeneic cells biochemically. Vanikar et al. conducted a study in which allogeneic ASC were coinfused with allogeneic hematopoietic stem cell transplantation; they found no evidence of graft versus host disease [82]. Zheng et al. described no side effects during allogeneic ASC infusion in the six treated patients [84]. Two adverse events were noted the first day (1 diarrhea and 1 skin rash) , both of which resolved by the next day.

Two case series evaluated the possibility of immune reaction by measuring the ratio of CD4/CD8. In the study by Park et al., it was shown that the ratio of CD4/CD8 did not change [45]. In the study by Lee et al., they found no immunological rejection responses in any of the subjects, based on the ratio of CD4-positive to CD8-positive T cells [55].

The remaining case series did not use any biochemical assays to evaluate the possible immune reaction. Fang et al. was the first to use allogeneic ASC for the treatment of steroid resistant graft versus host disease, and they presented a case series of six patients [81]. They noted no adverse events related to the ASC infusion. Fang et al. also conducted a study using allogeneic ASC obtained from haploidentical donors, and cells were infused intravenously for the treatment of chronic refractory immune thrombocytopenic purpura, also without any mention of adverse effects [83]. De la Portilla described the use of an immunological assessment, but it was not mentioned in the Results section [38]. It was described that two patients were withdrawn from the study due to adverse events possibly due to treatment (pyrexia and perianal abscess); however, in the setting of treating perianal fistulas these events cannot necessarily be attributed to the allogeneic cells used. Oner et al. presented their results of a phase I trial administering subretinal allogeneic ASC for treatment of advanced stage retinitis pigmentosa [86]. They included 11 patients and did not describe any form of immunological reaction.

In the present studies, only ASCs were administered in allogeneic fashion. Several different biochemical tests were applied in the studies of which the CD4/CD8, cytokine levels and unspecific IgM and IgG did not reveal any sign of activated immune response toward the foreign cells. Only the two studies testing for donor-specific antibodies revealed that 19%–34% of patients developed these which suggest that the cells are not as immune privileged as once thought. The consequences of these reactions are unknown.

Oncological Safety

The oncological safety was evaluated for studies administering cells in the setting of previous malignancy (Table 1). This included five studies (all case series) with a follow-up in the range of 3–12 months. Perez-Cano et al. published a study including 67 patients where ADRC were injected into patients with previous breast cancer, where treatment was given as a cell-assisted lipotransfer [27].

Table 1. Overview of safety analysis regarding thromboembolic safety and mortality, immunological as well as oncological safety

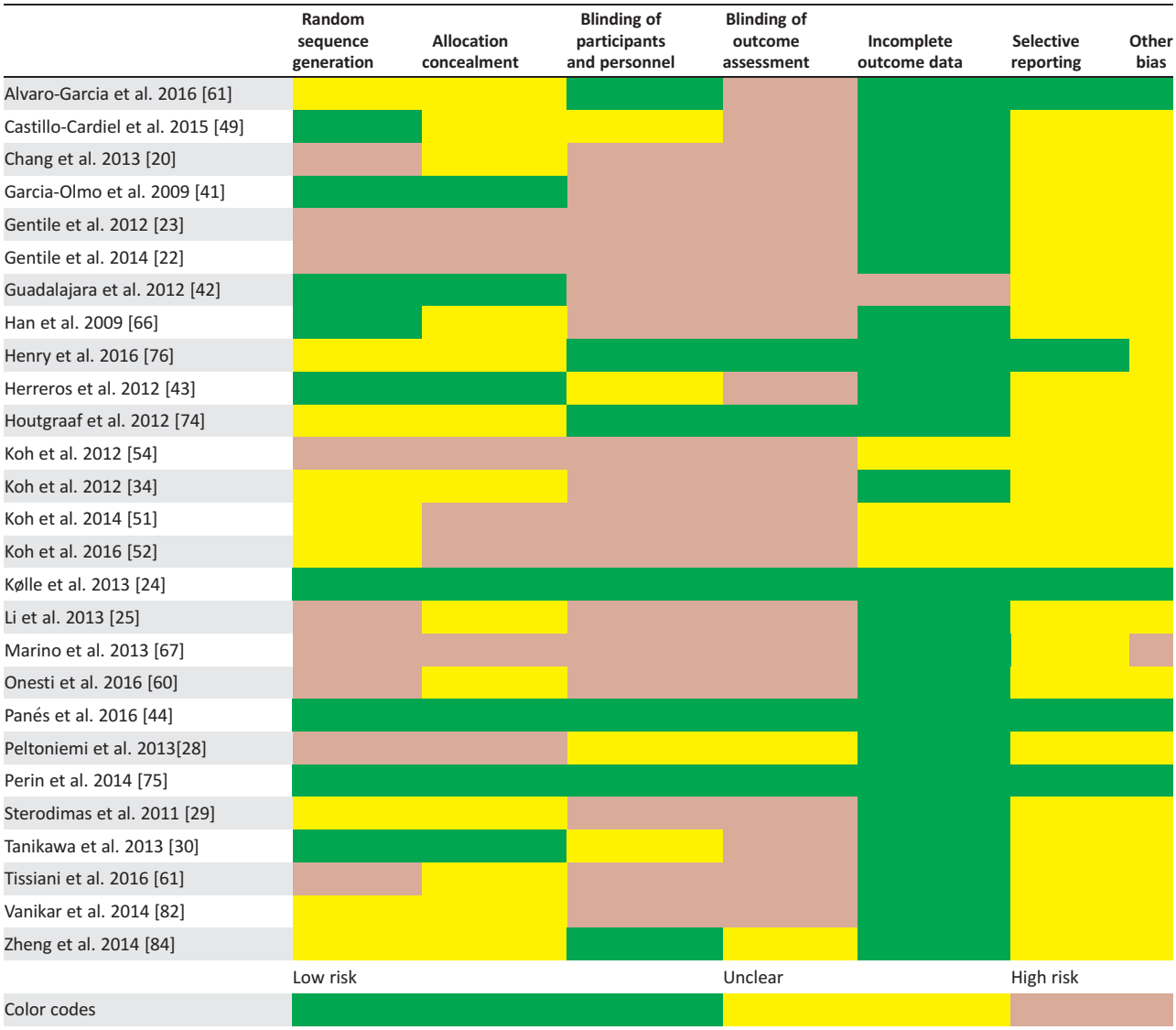
Thromboembolic safety and mortality						
Author	**Study type**	**Administration route**	**Cell type**	**TE complications**	**Mortality**	**Follow-up**
Cardiac						
Comella et al. [73]	Case series	Transendocardial	ADRC	1/28	3/28	6
Henry et al. [76]	RCT	Intramyocardial	ADRC	3/17 (1/14)	2/17 (0/14)	12
Houtgraaf et al. [74]	RCT	Intracoronary	ADRC	–	–	6
Perin et al. [75]	RCT	Transendocardial	ADRC	1/21 (1/6)	3/21 (2/6)	36
Immunological						
Vanikar et al. [82]	RCT	Intravenous	alloASC	6/95 (9/190)	7/95 (20/190)	6
Fang et al. [81]	Case series	Intravenous	alloASC	0/6	2/6	40
Fang et al. [83]	Case series	Intravenous	alloASC	0/7	0/7	8
Pulmonary						
Zheng et al. [84]	RCT	Intravenous	alloASC	0/6 (0/6)	1/6 (2/6)	1
Rheumatological						
Álvares Garcia et al. [61]	RCT	Intravenous	alloASC	1/46 (0/7)	0/46 (0/7)	6

Immunological safety						
Author	**Study type**	**Administration route**	**Cell type**	**Complications**	**Biochemical reaction**	**Follow-up**
Gastrointestinal						
Park et al. [45]	Case series	Wall of fistula	alloASC	0/6	CD4/CD8: N.s.i.	6
Panés et al. [44]	RCT	Wall of fistula	alloASC	N.d.	ASC/HLA-I: 34%	6
Garcia-Arranz et al. [39]	Case series	Wall of fistula	alloASC	0/10	Cytokine/US: N.s.i.	12
De la Portilla et al. [38]	Case series	Wall of fistula	alloASC	Fever: 1/24	–	4
Immunological						
Fang et al. [83]	Case series	Intravenous	alloASC	0/7	–	8
Fang et al. [81]	Case series	Intravenous	alloASC	0/6	–	40
Vanikar et al. [82]	RCT	Intravenous	alloASC	N.d.	–	6
Muskuloskeletal						
Lee et al. [55]	Case series	Intratendinous	alloASC	0/12	CD4/CD8: N.s.i.	12
Ophthalmological						
Oner et al. [86]	Case series	Subretinal	alloASC	0/11	–	6
Pulmonary						
Zheng et al. [84]	RCT	Intravenous	alloASC	0/6 (0/6)	–	1
Rheumatological						
Álvaro-Gracia et al. [61]	RCT	Intravenous	alloASC	Fever: 9/46 (0/7) Infections: 20/46 (0/7) Rash: 2/46 (0/7)	ASC/HLA-I: 19%.	6

Oncological Safety						
Author	**Study type**	**Administration route**	**Cell type**	**Local recurrence**	**Metastasis**	**Follow-up**
Soft tissue, breast						
Aronowitz et al. [19]	Case series	Subcutaneous	ADRC	1/54	0/54	12
Pérez-Cano et al. [27]	Case series	Subcutaneous	ADRC	0/67	1/67	12
Urogenital						
Choi et al. [72]	Case series	Transurethral	ADRC	0/6	0/6	3
Gotoh et al. [68]	Case series	Periurethral	ADRC	0/9	0/9	6
Haahr et al. [70]	Case series	Corpus cavernosum	ADRC	0/17	0/17	6

Abbreviations: –, not described/not performed; CD4/CD8, CD4 to CD8 ratio; N.d., no difference in adverse events between groups. no immunological adverse events; N.s.i., no sign of immune rejection; alloASC, allogeneic ASC; ASC/HLA-I, ASC-specific anti-HLA-I antibodies; Cell type, ADRC were autologous in all cases; cytokine/US, cytokine and unspecific antibodies. Data shown as treatment group count/total (control count/total); mortality, all-cause mortality; TE, thromboembolic.

Table 2. Risk of bias analysis



All studies with a control group were included for the analysis. Green: Low risk of bias, Yellow: Unclear risk of bias, Red: High risk of bias.

Herein no cases of local recurrence were described, but one case of pelvic metastasis was observed without exact note of timing. Four other serious adverse events were noted; however, only one of these was described, which was donor site bleeding following liposuction. In another study, Aronowitz et al. found that of the 54 patients with previous breast cancer, one patient developed a recurrence after cell-assisted lipotransfer with ADRC 11 months after treatment [19].

A study by Gotoh et al. gave a similar treatment with ADRC as a cell-assisted lipotransfer for urinary incontinence, in which 9/11 patients were previously treated for prostate cancer [87]. Here they found no evidence of recurrence during the 1-year follow-up. In a similar population group Haahr et al. injected ADRC intracavernosal to patients with erectile dysfunction due to previous prostate cancer surgery [70]. The authors did not describe any case of recurrence in their 6-month follow-up study. Similarly, to treat urinary incontinence following prostatectomy, Choi et al. administered ADRC as a cell-assisted lipotransfer to six patients [72]. They described no cases of recurrence or any other side effects in their 3-month follow-up study.

All studies included in the evaluation of oncological safety used autologous ADRC for treatment. There was only one case of local breast cancer recurrence out of a total of 121 patients across two studies within the 12-month follow-up periods. The remaining three studies applied ADRC in 32 previous prostate cancer patients and observed no recurrences within the follow-up period, ranging from 3 to 6 months. For determining long-term oncological safety, follow-up periods of several years are necessary to ensure that cell therapy is safe.

Bias

All studies with a comparison group were included in the analysis for bias looking specifically at the safety outcome (Table 2); 27 studies were eligible for inclusion. Only seven studies had proper randomization and allocation concealment. For the outcome safety, only five studies described proper blinding of patient, personnel and outcome assessor. Three of these studies were with ADRC and described proper blinding with the introduction of liposuction and subsequent sham ADRC injection [74–76].

Discussion

The clinical translation process of adipose-derived cell products has begun, and it is crucial that implementation of cell therapy is based on the standard principles of evidence-based medicine. Presently, cell therapy is widely considered as being equivalent to pharmaceutical drugs, which implies that cell therapies should adhere to the same standards for implementation as any newly developed drug, including the assessment of safety and adverse events.

This review includes more than 1,400 patients treated with adipose-derived cell therapy with follow-up ranging from less than a month to 3 years [75, 84]. Very few adverse events have been reported that can be related directly to the cell therapy, Events were rather related to the harvesting of adipose tissue, trauma associated with injection, or the nature of the underlying condition being treated. Of all studies administering ASCs systemically, a case of pulmonary thromboembolism [73], as well as cases of myocardial and cerebral infarctions were described [75, 76]. These are serious adverse events that can be fatal and since there is no clear clinical evidence for the efficacy of adipose-derived cell therapy as of yet, future studies administering cells systemically should be cautious and monitor for these possible serious adverse events. The studies did not describe whether the cells were filtered before administration to ensure that the injected cells were single cell suspensions. Thromboembolic complication risk can be assumed to be higher when injecting clumped cells compared with single cell suspensions. In addition, the underlying condition must also be taken into account as the included patients had a poor prognosis.

Several studies used allogeneic ASC treatment and there was no clear evidence of a clinical immune response. However, for studies examining the presence and later production of donor-specific antibodies, 19%–34% of patients developed these antibodies suggesting that indeed there is a cellular response occurring toward the allogeneic cells [44, 61]. The consequence of this, if any, still remains unknown. In many instances it can be questioned whether the use of allogeneic ASCs has any value over autologous cells, as many of the treated conditions are not acute and life threatening, leaving room and time for the easy, simple isolation and culture-expansion of ASCs. The use of ADRCs has the advantages of being completely autologous and requires much less advanced facilities as treatment can be offered as a same day procedure with everything needed being available in the operating theatre [88]. On the other hand, the advantage of ASCs is the fact that an almost unlimited number of cells can be obtained and is also a more realistic option if one was to consider cell banking either as autologous or allogeneic treatment modalities, and already some studies have been published with funding from companies seeking to offer off-the-shelf allogeneic ASC therapy [44, 61].

Another concern is the use of cell therapy in areas with previous malignancy, as preclinical data have suggested that cell therapy can aggravate any remaining cancer cells [12–14]. However, this has so far not been shown in the clinical setting, as we only could identify one case of recurrence following cell-assisted lipotransfer among 121 breast cancer patients, which is well within what could be expected [89]. It is vital in the setting of previous cancer treatment that safety evaluations are conducted thoroughly with sufficiently long follow-up times, so these initial uplifting results can be confirmed.

During the last 5 years, there has been a marked increase in the number of adipose-derived cell therapy clinical trials that have been published; however, at present most of them are at the case series level (Level IV evidence). In general, it is recognized that low quality studies increase risk of bias, which leads to an increasing chance of findings that do not represent reality [90]. Therefore, it is important to transition toward well-conducted randomized controlled trials with adequate blinding, which also includes the safety assessment.

A systematic review can only be as good as the available literature allows it to be, and this review was limited by the fact that so many studies did not clearly describe their method of assessing safety, and in the end, you will only find the adverse events that you are looking for. Another limitation of the review is the possibility of small overlap in some of the included studies, as case series were published over time from the same research groups with an increasing number of patients; this was deemed to be of such a small magnitude that it was insignificant.

While adipose-derived cell therapy has shown great potential so far, there is very sparse clinical evidence to promote routine clinical implementation. There is a need for higher quality studies before rational conclusions can be made regarding the efficacy of adipose-derived cell therapies. Future studies should place a larger emphasis on including a placebo/sham treatment for proper blinding of both patients and assessors. This is especially crucial when the primary outcome is subjective due to the placebo response [91].

Author Contributions

N.T., M.J., S.T., and J.S.: conception and design; N.T., S.P., and J.S.: financial support; S.P. and J.S.: administrative support; N.T., M.J., and S.T.: provision of study material or patients; N.T., M.J., S.T., and C.J.: collection and/or assembly of data, data analysis and interpretation; N.T., M.J., and S.T.: manuscript writing; N.T., M.J., S.T., C.J., and S.P.: final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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