Clin Exp Metastasis (2012) 29:681–686
DOI 10.1007/s10585-012-9497-x

RESEARCH PAPER

The efficacy of Tilmanocept in sentinel lymph mode mapping and identification in breast cancer patients: a comparative review and meta-analysis of the ^{99m}Tc-labeled nanocolloid human serum albumin standard of care

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Received: 18 May 2012 / Accepted: 28 May 2012 / Published online: 23 June 2012

Abstract Sentinel lymph node (SLN) mapping is common, however question remains as to what the ideal imaging agent is and how such an agent might provide reliable and stable localization of SLNs. ^{99m}Tc-labeled nanocolloid human serum albumin (Nanocoll®) is the most commonly used radio-labeled colloid in Europe and remains the standard of care (SOC). It is used in conjunction with vital blue dyes (VBDs) which relies on simple lymphatic drainage for localization. Although the exact mechanism of Nanocoll SLN localization is unknown, there is general agreement that Nanocoll exhibits the optimal size distribution and radiolabeling properties of the commercially available radiolabel colloids. [^{99m}Tc]Tilmanocept is a novel radiopharmaceutical designed to address these deficiencies. Our aim was to compare [^{99m}Tc]Tilmanocept to Nanocoll for SLN mapping in breast cancer. Data from the Phase III clinical trials of [^{99m}Tc]Tilmanocept's concordance with VBD was compared to a meta-analysis of a review of the literature to identify a ^{99m}Tc albumin colloid SOC. The primary endpoints were SLN localization rate and degree of localization. Six studies were used for a meta-analysis to identify the colloid-based SOC. Five studies (6,134 patients) were used to calculate the SOC localization rate of 95.91 % (CI 0.9428–0.9754) and three studies (1,380 patients) were used for the SOC SLN degree of localization of 1.6683 (CI 1.5136–1.8230). The lower bound of the confidence interval was used for comparison to Tilmanocept. Tilmanocept data included 148 patients, and pooled analysis revealed a 99.99 % (CI 0.9977–1.0000) localization rate and degree of localization of 2.16 (CI 1.964–2.3600). Tilmanocept was superior to the Nanocoll SOC for both endpoints ($P < 0.0001$).

Keywords [^{99m}Tc]Tilmanocept · ^{99m}Tc-labeled nanocolloid human serum albumin · Nanocoll® · Sentinel lymph node · Breast cancer · Lymphoscintigraphy

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Introduction

In patients with breast cancer, lymph node status is a strong predictor of long-term patient outcome. Importantly, such pathology status defines patient staging and strongly influences the course of treatment a patient may follow after surgery [1, 2]. In an effort to reduce the morbidity and costs of detection of lymph node metastases, surgical oncologists have developed a method by which sentinel lymph nodes (SLNs) are identified intra-operatively and removed. The concept of the SLN was first described in 1992 by Morton et al. [3] with the use of vital blue dye

(VBD) to identify the first draining node in a lymphatic basin in patients with melanoma The concept assumes that lymphatic tumor spread occurs in the first draining lymph node, the SLN, prior to spreading to subsequent nodes. If negative for tumor metastasis, the procedure has been used in lieu of complete regional lymphadenectomy and has been validated in breast cancer to be predictive of axillary nodal status, with a false negative rate of less than 5 % [4–6]. Despite the widespread use of the sentinel lymph node biopsy (SLNB) for axillary staging of breast cancer, question still remains as to the optimal agent for SLN identification.

An ideal lymph node imaging agent would exhibit rapid clearance from the injection site, rapid uptake and high retention within the first draining lymph node, as well as low uptake by the remaining lymph nodes [7]. The ideal agent would have low radiation absorption, high biological safety, rapid and stable technetium-99m labeling, and radiochemical purity. [^{99m}Tc]Tilmanocept is a novel radiopharmaceutical that has been studied for the use in SLN identification. It accumulates in lymphatic tissue by avidly binding to receptors that reside on the surface of dendritic cells and macrophages [7–9]. [^{99m}Tc]Tilmanocept, also known as Lymphoseek®, exhibits sub-nanomolar affinity ($K_D = 0.25$ nM) to the receptor (CD206) and has a mean molecular diameter of 0.007 μm.

VBD was the first agent used in SLN identification [3], but the procedure has become more sensitive and specific when used in conjunction with a radiopharmaceutical [10, 11], which is now commonly used. In the United States, ^{99m}Tc-labeled sulfur colloid, which was initially designed and approved for liver and spleen imaging, is used unfiltered or after filtration through a 0.10- or 0.22-μm syringe filter. The particle size range of unfiltered ^{99m}Tc-labeled sulfur colloid is 0.015–5 μm, and the size range of filtered ^{99m}Tc-labeled sulfur colloid is 0.05–0.10 or 0.05–0.20 μm depending on the filter [12]. Technetium-99m-labeled antimony trisulfide (Lymph-Flo®) is available in Australia and Canada and exists as the smallest particles, ranging from 0.003 to 0.030 μm [13].

Technetium-99m-labeled nanocolloid human serum albumin (Nanocoll®) is the most commonly used radiocolloid in Europe. Although Nanocoll was initially designed and approved for inflammation and bone marrow imaging after intravenous administration, and lymphatic channel imaging after cutaneous administration, it has an favorable particle size range for SLN mapping [14]. Particles between 0.004 to 0.10 μm in size provide a balance between rapid lymph channel entry and sustained SLN retention with minimal passage to distal lymph nodes. In addition to its favorable size, Nanocoll exhibits superior radiochemical properties [14]; radio-labeling yields of 98–99 % are routine (i.e. 1–2 % of the radioactivity is attached to the colloid) [12]. Filtration of ^{99m}Tc-labeled sulfur colloid typically results in radiochemical purities in the 90 to 92 % range [15]. The fact that 8–10 % of the radioactivity is not attached to the colloid means that the very small radioactive particles can rapidly enter the lymph channels and pass through the chain of lymph nodes. For these reasons Mariani et al. [14]. considered Nanocoll to be the optimal radio-colloid for SNL mapping. We, therefore, have selected Nanocoll as the best benchmark to compare the performance of the molecular imaging agent, [^{99m}Tc]Tilmanocept.

The purpose of this retrospective meta-analysis was to compare the efficacy of ^{99m}Tc-labeled nanocolloid human serum albumin (Nanocoll®) and [^{99m}Tc]Tilmanocept. We combined Nanocoll data from recent clinical SLN mapping studies in patients with known breast cancer and compared two efficacy metrics from two Tilmanocept Phase III clinical trials.

Methods

We performed a retrospective comparison study of [^{99m}Tc]Tilmanocept to an ^{99m}Tc nanocolloid human serum albumin standard of care (SOC) in the in vivo detection of lymph nodes in breast cancer patients who underwent intraoperative lymphatic mapping. There were two components of this retrospective review. The first was to perform an extensive review of the literature regarding the clinical experience in SLN mapping using ^{99m}Tc albumin colloid, and the second, to analyze the data from the two completed Phase III clinical studies of [^{99m}Tc]Tilmanocept in breast cancer patients, NEO3-05 and NEO3-09. Our primary outcome measure for comparison was the localization rate of the mapping agent defined as the proportion of patients with at least one localized lymph node. The second endpoint for comparison was the average number of localized nodes relative to the patient population.

Tilmanocept Phase III data—population and performance analysis

The [^{99m}Tc]Tilmanocept clinical trials were all approved by appropriate ethical committees and institutional review boards. The efficacy analyses relative to Tilmanocept has summarized data from the two pivotal Phase III efficacy studies completed for Tilmanocept, NEO3-05 (initiated in May 2008, completed in June 2009) and NEO3-09 (initiated in July 2010, completed in April 2011). Both represent multi-center, prospective, randomized clinical trials designed to test the efficacy of Tilmanocept relative to VBD at SLN identification. The study population was defined as those protocol eligible breast cancer patients enrolled in either of the above clinical trials, were injected

Table 1 Summary of ^{99m}albumin colloid standard of care

Article citation	Number of patients	Localization rate	95 % CI for rate	Degree of localization	95 % CI for degree of localization
Bulte et al. [26]	595	0.9899	(0.9782, 0.9963)	1.6	(1.5462, 1.6538)
Doting et al. [20]	126	Na	Na	1.7	(1.6127, 1.7873)
Heuts et al. [27]	656	0.9741	(0.9588, 0.9848)	Na	Na
Konstantiniuk et al. [28]	2,271	0.9419	(0.9314, 0.9511)	Na	Na
Langer et al. [29]	659	0.9833	(0.9703, 0.9916)	2.1	(1.9221, 2.2779)
Straver et al. [19]	1,953	0.9667	(0.9578, 0.9742)	Na	Na

Na not applicable

with Tilmanocept, went to surgery, and had intra-operative gamma survey completed. Subjects from the NEO3-05 sites 05 and 06 were excluded from the analysis secondary to injection volume dilution practiced specifically by the investigators at those sites.

Retrospective review—^{99m}Tc nanocolloid human serum albumin SOC benchmark

A comprehensive search of the clinical practice literature was conducted in order to select studies to be included in the meta-analysis for a ^{99m}Tc nanocolloid human serum albumin SOC benchmark. The search focused on articles published in oncology and surgery-related peer reviewed journals within the last 10 years in order provide an accurate representation of the current SOC. Each study included in the meta-analysis reported on at least one of two of our applicable outcomes measures, as well as met specific criteria reflective of the inclusion criteria for the Tilmanocept Phase III clinical trials in order to ensure similarity among patient populations. Specific inclusion criteria on populations studied included patients with primary breast cancer, patients at least 18 years of age, ECOG status of Grade 0–2, clinically negative node status at time of study entry (Tis-T4, N0, M0), and patients that received a lymphatic mapping agent prior to SLN mapping. A total of 6 studies met the above inclusion criteria and are summarized in Table 1.

Statistical analysis

The primary efficacy endpoint was the localization rate of the mapping agent relative to the study population and the secondary primary efficacy endpoint was the degree of localization measured by the average number of localized nodes per patient relative to the study population. These were calculated for the Tilmanocept population, and 95 % exact confidence intervals were computed. For all endpoints, a meta-analysis and a pooled analysis was performed. As these studies were similarly designed and contain similar patient populations, a fixed effects meta-analysis model was used.

A random effects meta-analysis model that allows for between-study variability was used to combine the localization rate estimates and the degree of localization estimates from the historical studies. A weighted least squares (WLS) analyses was used to produce the overall estimate of the localization rate based on data from the selected studies and compute a 95 % exact confidence interval. The lower bound of the confidence interval served as the estimate for each study in the retrospective review.

Historical benchmark values were then compared to results from the pooled and fixed effects meta-analysis of Tilmanocept patients for the primary and secondary efficacy endpoints and *P* values were obtained.

Results

[^{99m}Tc]Tilmanocept

A total of 148 patients were identified from NEO3-05 and NEO3-09 trials and included in the Tilmanocept comparison population. 146 of these patients had one or more localized lymph nodes, resulting in a localization rate of 99.99 % (CI 0.9977–1.0000) on meta-analysis and 98.65 % (CI 0.9520–0.9984) on pooled analysis. Degree of Tilmanocept SLN localization was calculated at 2.08 (CI 1.9052–2.2626) and 2.16 (1.964–2.3600) for meta- and pooled analysis respectively.

^{99m}Tc albumin colloid-SOC benchmark review

A total of 6 studies met inclusion criteria for meta-analysis. 5 of these studies contained data sufficient to calculate a localization rate, a summary of which is contained in Table 1. Meta-analysis of this data contained a total of 6,134 patients, with a random effects model revealing a localization rate of 95.91 % (CI 0.9428–0.9754). As described above, the lower bound of the 95 % CI was used

Table 2 Tilmanocept combined Phase III clinical data versus SOC

	Meta-analysis ($N = 148$)	Pooled analysis ($N = 148$)
Number (proportion) of localized patients	146 (0.999)	146 (0.9865)
95 % Confidence interval	(0.9977, 1.000)	(0.9520, 0.9984)
P value (localization rate versus SOC LR $\leq$ 0.9428)	<0.0001	0.0082
P value (degree of localization versus SOC DL $\leq$ 1.5136)	<0.0001	<0.0001

LR localization rate, *DL* degree of localization

as the benchmark. This was compared to the Tilmanocept meta-analysis and pooled analysis, revealing that Tilmanocept had a significantly superior SLN localization rate ($P < 0.0001$, $P = 0.0082$, respectively).

A total of 3 of the 7 studies that met inclusion criteria for meta-analysis contained sufficient data to calculate the degree of localization, summary of which is also contained in Table 1. Meta-analysis of this data contained a total of 1,380 patients, with a random effects model revealing a degree of localization of 1.6683 (CI 1.5136–1.8230). Using the lower bound of the CI, compared to Tilmanocept meta-analysis and pooled analysis, Tilmanocept had a significantly superior SLN degree of localization ($P < 0.001$, $P < 0.001$, respectively). For a summary of comparisons, please see Table 2.

Tilmanocept was superior to the Nanocoll meta-analysis SOC benchmark in all endpoints evaluated (see Fig. 1).

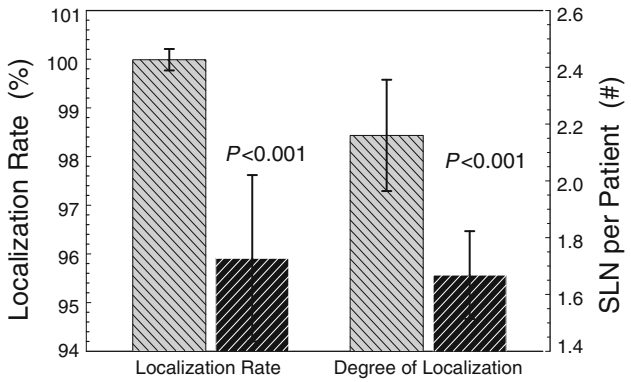

Fig. 1 Tilmanocept demonstrated higher sentinel lymph node localization rate and degree of localization than Nanocoll, the albumin-colloid standard of care benchmark. The novel radiopharmaceutical [^{99m}Tc]Tilmanocept is represented in *grey*, while ^{99m}Tc-labeled nanocolloid human serum albumin (Nanocoll) meta-analyses benchmark is represented in *black*. Localization rate is defined as the proportion of patients with at least one localized lymph node, while degree of localization represents average number of localized node per patient

Discussion

The concept of the sentinel lymph node (SLN) was first described by Cabanas in 1977 [16], proposing that the first lymph node downstream from a tumor would be the first regional node affected by metastatic disease, and if negative, prevent the need for more extensive regional lymphadenectomy. Later studies by Morton et al. [3] a decade letter used vital blue dye (VBD) for lymphatic mapping and SLN identification in melanoma [3], and it has since been validated as a technique for predicting axillary nodal status in breast cancer, which is currently the most important prognostic indicator for future development of systemic disease [1, 2].

Currently, the technique of sentinel lymph node biopsy (SLNB) in breast cancer involves injection of a lymphatic mapping agent into the dermis or breast parenchyma [17], most commonly a combination of a VBD and a radiopharmaceutical, and the SLN is identified intra-operatively via direct visualization of a blue hue and/or signal with a handheld gamma probe.

Despite the widespread use of SLNB for axillary staging of breast cancer, question still remains as to what the optimal agent for SLN identification is. We have decided to focus our efforts on a comparison between Tilmanocept and Nanocoll, an agent that has been extensively studied and used in large prospective clinical trials [18–23]. Tilmanocept has been compared to ^{99m}Tc-labeled filtered sulfur colloid (fTcSC) in prior studies to varying extent [9], however this represents the first comparison of Tilmanocept with Nanocoll. Furthermore, confining the analysis to albumin-colloid will likely eliminate data heterogeneity caused by differences in the various colloidal mapping agents. While fTcSC is widely employed for lymphatic mapping in the United States, its preparation and administration is not standardized. Multiple preparations (i.e. particle size distributions) and administration techniques would broaden the standard deviations in the efficacy metrics and reduce the power of a meta-analysis. Additionally it is difficult in some publications to determine if filtered and/or unfiltered ^{99m}Tc-labeled sulfur colloid was used. For these reasons, we have decided to focus our attention to a comparison against Nanocoll®, which has a greater degree of standardized preparation.

Tilmanocept, [^{99m}Tc]diethylenetriamine pentaacetic acid (DTPA)-mannosyl-dextran, is a novel radiopharmaceutical synthesized as a specific SLN mapping agent designed to address the shortcomings of commonly used agents. Composed of a dextran backbone with multiple mannose subunits and DTPA side chains attached, it is a macromolecule with an average diameter of 7 nm [18]. Its size allows rapid lymphatic uptake, while its mannose subunits allow for cell specific binding of the mannose

receptor on macrophages and dendritic cells concentrated in lymph nodes, subsequently reducing diffusion into higher echelon regional nodes [7, 18]. This is in contrast to VBD and radio-labeled colloids that lack tissue-specific binding properties.

The NEO3-05 and NEO3-09 Phase III clinical trials were designed to evaluate concordance between Tilmanocept and VBD in breast cancer and melanoma patients, and have shown a 98 % concordance rate and a 0 % failed detection rate (FDR). Comparison to VBD was chosen as a primary endpoint as it remains a chemically standardized FDA-approved lymphatic mapping agent in the United States. While SLN identification has been validated in both melanoma and breast cancer, we have focused our comparison on SLN mapping agents in breast cancer because the disease offers large and recent prospective studies that allow for greater statistical power.

Safety was not an endpoint of this study; however it should be noted that Phase III clinical trials of Tilmanocept revealed an excellent safety profile, no serious adverse reactions, and no allergic reactions, in contrast to both colloidal albumin and VBD, where adverse and allergic reactions have been reported.

This study has limitations inherent in any retrospective review or meta-analysis. Meta-analysis pools data from multiple sources without removing individual study bias; however this was likely minimized by the random effects statistical model used. Furthermore, while many of the studies represented large multicenter trials, only Straver et al. [19] and Doting et al. [20] studied a similar primary outcome related to SLN identification. In addition, variability in injection practices and SLNB technique was not addressed. Tilmanocept is a new agent and data from the Tilmanocept prospective randomized trials represent a more recent experience, however, there have been no significant changes in SLNB technique, and the meta-analysis focused on recent literature to minimize this confounder. In addition, both the Tilmanocept and albumin-colloid studies were performed at large volume centers where surgeons likely surpassed the low number of SLNBs required to attain excellent success rates [21], minimizing inter-operator variation.

Furthermore, while the attempt was to compare Tilmanocept with radio-labeled colloids, all studies including Tilmanocept studies used VBD in conjunction with a radio-labeled agent. VBD is currently used in the majority of SLN procedures, and it would not be feasible to exclude VBD unless a prospective study was performed.

As mentioned above, Mariani et al. [14] have proposed that the particle size distribution and radio-labeling properties of Nanocoll make it the radio-pharmaceutical of choice for SLN mapping, however our findings suggest that Tilmanocept offers improved ability to detect the SLN, and its receptor-specific binding properties offer improved SLN localization. Since other radio-labeled colloids lack molecular binding properties and differ more substantially from the ideal size proposed by Mariani et al. [14] for lymphatic entry and SLN localization, we expect that comparing Tilmanocept to other commonly used SLN mapping agents would yield similar, if not more substantial improvements in SLN identification and localization. The significantly smaller particles that define antimony trisulfide would allow for quick lymphatic entry, but easy passage to higher echelon nodes increasing the probability of passing through the SLN and missing it altogether, thereby decreasing the sensitivity and specificity of the SLNB procedure. Large variations in particle size seen in unfiltered and filtered sulfur colloid, commonly used in the United States, decrease the agent's efficiency at entering lymphatic channels and localizing in SLNs, and despite the widespread use of filters to improve particle size distribution, there still remains controversy to whether unfiltered or filtered sulfur colloid is optimal [22, 23].

With over 200,000 new patients diagnosed with breast cancer each year in the United states [24], and over double that in Europe [25], the potential impact of a 2–3 % improvement in SLN identification as shown with Tilmanocept translates into 12,000–18,000 patients who could benefit from improved cancer staging and treatment, which could have profound implications on international practice patterns.

Acknowledgments We would like to acknowledge the technical assistance of Ms. Stephanie Dietz and Ms. Amy Bulgrin in the compilation of the data sets. This analysis supported by funds from Navidea Biopharmaceuticals.

Conflict of interest FOC is an employee and officer of Navidea Biopharmaceuticals. WLM is an employee of Navidea Biopharmaceuticals. MSB is an employee of Navidea Biopharmaceuticals. BCA is an employee of Navidea Biopharmaceuticals. DRV is the inventor of Tilmanocept. The remaining authors declare that they have no conflict of interest.

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