SAFETY AND EFFECTIVENESS OF GMP GRADE MONTANIDE™ ISA 51 VG ST ADJUVANT FOR THERAPEUTIC VACCINES

Hocine Nouari[1]; Marie-Eve Koziol [2]
[1] SEPPIC 22 Terrasse Bellini, Paris La Défense, 92807 Puteaux Cedex
[2] SEPPIC Inc, 30 Two Bridges Road, suite 210, Fairfield, New Jersey 07004

Introduction

Therapeutic cancer vaccines are one interesting alternative to treat cancer by active immunotherapy. As highly purified antigens are poorly immunogenic, adjuvants can be associated to elicit an early, high and long-lasting immune response. Among the tested adjuvants, MONTANIDE™ ISA 51 VG ST shows a strong safety and effectiveness profile based on clinical trials results. Indeed, MONTANIDE™ ISA 51 VG ST is formulated in many vaccines candidates, and tested in both preclinical and clinical trials. A relevant example is that MONTANIDE™ ISA 51 VG ST is already included in a therapeutic vaccine against non small cell lung cancer (NSCLC) approved in seven countries.

Our objective is to revisit the safety of MONTANIDE™ ISA 51 VG ST based on clinical trials records, and to highlight its effectiveness as adjuvant for therapeutic vaccines, especially in cancer active immunotherapy.

Background

Figure 1: W/O structure emulsion and mechanism of immune stimulation

MONTANIDE™ ISA 51 VG ST formulated with antigens produces a water in oil emulsion (W/O) known to enhance the immune response of therapeutic vaccines. When injected, emulsions create a depot effect and allow a slow release of the antigen and may also protect it from degradation by proteolysis. Vaccines based on MONTANIDE™ ISA 51 VG ST induce a danger signal and enhance interaction between antigen and Antigen Presenting Cells (APC) like Dendritic cells (DC). Antigen is released and uptaken by APC.

→ Adjuvant and antigen are processed by APC to initiate maturation and migration processes to the Lymph Node.

Safety of MONTANIDE™ ISA 51 VG ST

A total of 125 clinical trials including MONTANIDE™ ISA 51 VG ST were published representing 6000+ vaccinated patients. Most of vaccines were injected subcutaneously, except for AIDS projects (Kahn, 2000), for which intramuscular route was used.

Local and general reactions were observed but did not lead to patient withdrawal. The reactions observed are transients and of mainly mild to moderate intensity. Indeed, local reactions described were generally erythema, local pain or granuloma (Celis, 2008), swelling or discomfort (Sosman, 2009). General reactions were mostly flu like symptoms, fever and nausea (Nishida, 2014). Low frequency grade III reactions can be associated with high antigen concentration, important volume of injection (Takashi, 2004) or costimulation (Okada, 2014).

MONTANIDE™ ISA 51 VG ST can be used in chronic vaccinations without increasing side effects after 28 or more injections (Gonzalez, 2011). Phases III study have been completed in a melanoma multicenter trial (Schwartzentruber, 2011) or in non small cell lung cancer (NSCLC) (Fernandez Lorente, 2013) providing confirmation of the safety of MONTANIDE™ ISA 51 VG ST in larger number of patients as vaccinated and control groups presented consistent adverse events.

Table 1: Safety records of published clinical trials with MONTANIDE™ ISA 51 VG

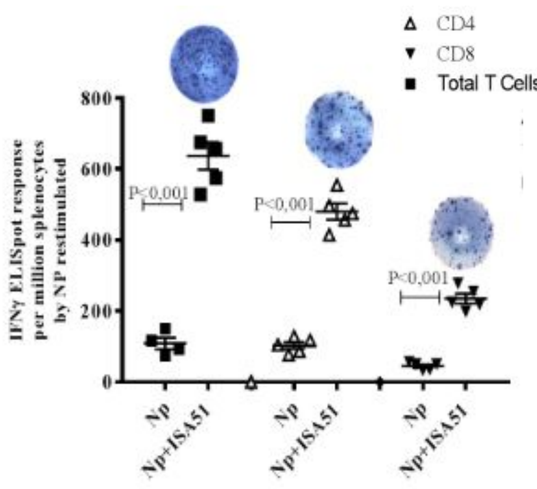
Cancer	Nr of publications	Clinical phase	Nr of patients	Intensity of local reactions	Intensity of general reactions
Melanoma	31	I/II/III	1169	I/II, 3 (III)	I/II, (2) III
NSCLC	7	I/II	667	I/II	I/II
Cervical	4	I/II	100	I/II	I
Colorectal	5	I	42	I/II	I
Leukemia	5	I/II	35	I/II	I
Gastric	2	I	19	I/II	I/II
Breast	3	II	75	I/II	I
Prostate	5	I/II	59	I/II	I
Ovarian	4	I/II	64	I/II	I
Various	16	I/II	224	I/II	I/II

Methods (table 1)

125 published clinical trials with these adjuvants are reviewed and the number of patients per indications are noticed, as well as the parameters of vaccination such as route of inoculation, volume, antigen dose, or co-stimulating agents. Safety data obtained are reviewed and are classified according to their nature type, and intensity.

Enhanced Immune Response with Montanide™ ISA 51 VG ST

Figure 2: T cells response after vaccination with MONTANIDE™ ISA 51 VG ST



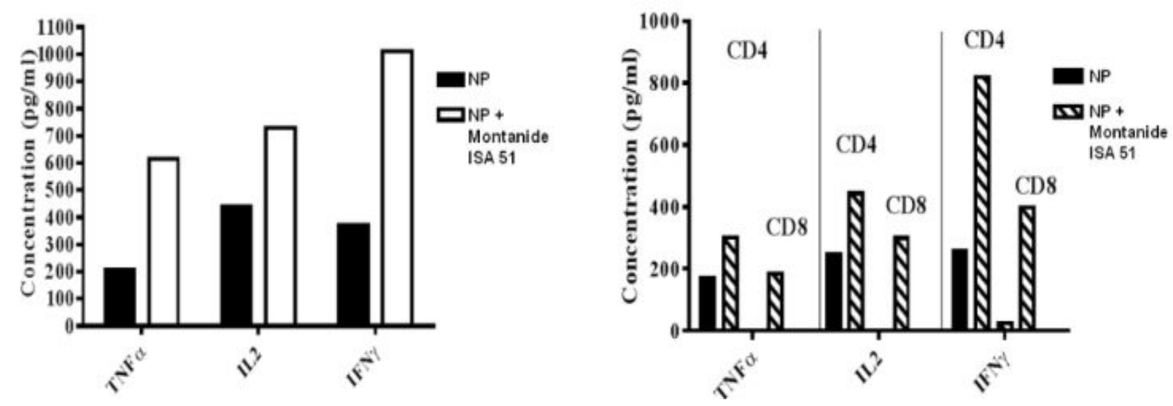
NP* + MONTANIDE™ ISA 51 VG ST

We observed a significant increase of T cells population in addition to an increase of IFNɣ

* Nuclear protein

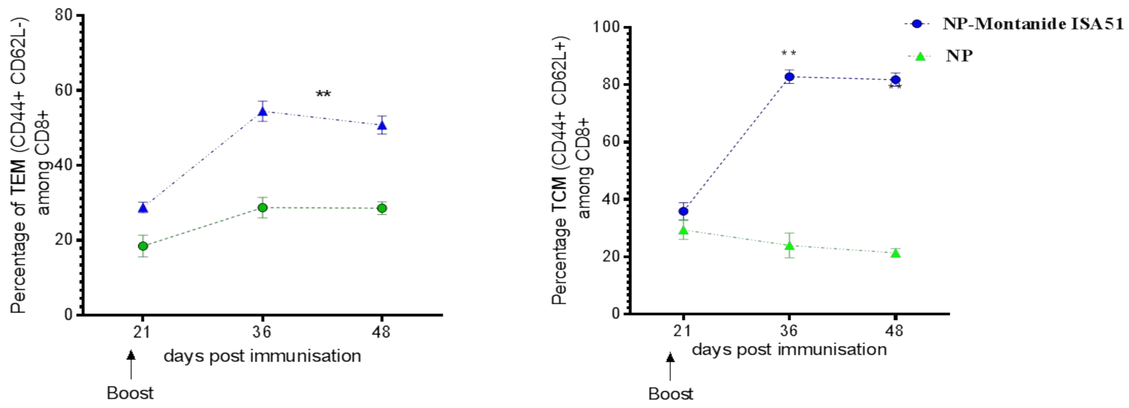
- **Increase of IFNɣ**
- **Increase of CD4**
- **Increase of CD8+**

Figure 3: T cells response after vaccination with MONTANIDE™ ISA 51 VG ST



Mice immunised with NP + MONTANIDE™ ISA 51 VG ST show an increase in TNFα, IL-2, IFNɣ cytokine secretion compared to control (no MONTANIDE™ ISA 51 VG ST).

Figure 4: TCM (CD44+ CD62L+) and TEM (CD44+ CD62L-) sub-population in mice vaccinated with or without MONTANIDE™ ISA 51 VG ST



Mice immunised with NP (nuclear protein) antigen + MONTANIDE™ ISA 51 VG ST elicit higher amount of effector memory T Lymphocytes and central memory T Lymphocytes compared to NP antigen alone.

- TCM role is to provide protection from a systemic challenge and is able to generate a second wave of effector cells.
- TEM function as sentinels for immediate protection from a peripheral challenge.

Methods (Figure 2, 3, 4)

5 C57BL/6 mice per group are vaccinated subcutaneously with 25µg of nucleoprotein (NP) alone or with MONTANIDE™ ISA 51 VG ST at weeks 0, 3. At week 5 splenocytes are sampled. T-cells are put in culture for 48h and stimulated with NP antigen.
IFNɣ response is followed by ELISpot. (Fig 2).
Cytokine secretions into the medium were measured by ELISA (Fig 3).
Specific memory CD8 T-cells populations are evaluated by flow cytometry (fig 4).

Conclusions

MONTANIDE™ ISA 51 VG ST is a well documented adjuvant intended to be used in therapeutic vaccination programs. MONTANIDE™ ISA 51 VG ST is known as a strong inducer of early high and long lasting cell mediated immune response.

MONTANIDE™ ISA 51 VG ST provide a safe vaccinal environment and is suitable for registration by agencies. MONTANIDE™ ISA 51 VG ST is included into CIMAVax EGF a NSCLC vaccine registered in 7 countries.

xxxx/GB:01/August 2018

Questions ?
Marie-eve.Koziol@airliquide.com