Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A systematic review and meta-analysis on the safety of newly adjuvanted vaccines among older adults ☆

Marc Baay, Kaatje Bollaerts, Thomas Verstraeten *

P95, Epidemiology and Pharmacovigilance Consulting and Services, Leuven, Belgium

ARTICLE INFO

Article history:
Received 16 March 2018
Received in revised form 31 May 2018
Accepted 1 June 2018
Available online xxxx

Keywords:
Vaccine
Adjuvants
Safety
Older adults

ABSTRACT

Introduction: New adjuvants have been developed to improve the efficacy of vaccines and for dose-sparing capacity and may overcome immuno senescence in the elderly. We reviewed the safety of newly-adjuvanted vaccines in older adults.

Methods: We searched Medline for clinical trials (CTs) including new adjuvant systems (AS01, AS02, AS03, or MF59), used in older adults, published between 01/1995 and 09/2017. Safety outcomes were: serious adverse events (SAEs); solicited local and general AEs (reactogenicity); unsolicited AEs; and potentially immune-mediated diseases (pIMDs). Standard random effects meta-analyses were conducted by type of safety event and adjuvant type, reporting Relative Risks (RR) with 95% confidence intervals (95% CI).

Results: We identified 1040 publications, from which we selected 7, 7, and 12 CTs on AS01/AS02, AS03 and MF59, respectively. 47,602 study participants received newly-adjuvanted vaccine and 44,521 control vaccine, or placebo. Rates of SAEs (RR = 0.99, 95% CI = 0.96–1.02), deaths (RR = 0.99, 95% CI = 0.92–1.06) and pIMDs (RR = 0.94, 95% CI = 0.79–1.1) were comparable in newly-adjuvanted and control groups. Vaccine-related SAEs occurred in <1% of the subjects in both groups. The reactogenicity of AS01/AS02 and AS03 adjuvanted vaccines was higher compared to control vaccines, whereas MF59-adjuvanted vaccines resulted only in more pain. Grade 3 reactogenicity was reported infrequently, with fatigue (RR = 2.48, 95% CI = 1.69–3.64), headache (RR = 2.94, 95% CI = 1.24–6.95), and myalgia (RR = 2.68, 95% CI = 1.86–3.80) occurring more frequently in newly-adjuvanted groups. Unsolicited AEs occurred slightly more frequently in newly-adjuvanted groups (RR = 1.04, 95% CI = 1.00–1.08).

Conclusions: Our review suggests that, within the clinical trial setting, the use of new adjuvants in older adults has not led to any safety concerns, with no increase in SAEs or fatalities. Higher rates for solicited AEs were observed, especially for AS01/AS02 and AS03 adjuvanted vaccines, but AEs were mostly mild and transient. Further evidence will need to come from the use of new adjuvants in the real-world setting, where larger numbers can be studied to potentially detect rare reactions.

1. Introduction

Several new adjuvants have been developed to improve the efficacy of vaccines and for dose sparing capacity. New adjuvants that are licensed or in advanced clinical development are AS01, AS02, AS03, AS04 and MF59. The Novartis-developed MF59® adjuvant is a squalene-based oil-in-water based adjuvant. The GlaxoSmithKline (GSK)-developed Adjuvant Systems (AS) are based on a combination of immuno-stimulants in different adjuvant formulations: AS01 contains 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL) and the saponin QS-21 and is a liposome-based formulation; AS02 also contains MPL and QS-21 and is an oil-in-water emulsion-based formulation. AS03 is composed of α-tocopherol, squalene and polysorbate 80 in an oil-in-water emulsion. Finally, AS04 is a combination of aluminum hydroxide and MPL [1–3].

These new adjuvants are increasingly being used across the entire age range. MF59 was first approved in 1997 as part of the trivalent influenza vaccine FLUAD. More recently, FLUAD was approved for use in adults over 65 in the US [4], and adults over 75 in the UK [5]. The first AS-adjuvanted vaccine was Fendrix, which includes AS04 and was approved in Europe in 2005 for the prevention of infections with hepatitis B virus in adolescents and

☆ Statement about prior postings and presentations: Neither this manuscript nor any similar paper is under consideration by any other scientific journal. Preliminary data have been submitted for presentation at the ICPE 2018 conference in Prague.

* Corresponding author at: P95, Epidemiology and Pharmacovigilance Consulting and Services, Koning Leopold III Laan 1, 3001 Leuven, Belgium.
E-mail address: Thomas.verstraeten@P-95.com (T. Verstraeten).

https://doi.org/10.1016/j.vaccine.2018.06.004
0264-410X/

adults [6]. Cervarix, another AS04-adjuvanted vaccine, was approved in Europe in 2007 for the prevention of premalignant anogenital lesions and cancers causally related to oncogenic HPV types in people aged 9–14 (two doses), whereas those aged 15 and above should receive three doses [7]. More recently, Mosquirix, a vaccine for the prevention of malaria which includes AS01 and was originally developed in combination with AS02, was approved in 2015 for use in children aged between 6 weeks and 17 months [8]. Finally, Shingrix, a vaccine which includes AS01 as adjuvant, was approved in March 2018 in the European Union, for the prevention of Herpes Zoster and post-herpetic neuralgia, for adults aged 50 years and older [9]. The use of new adjuvants appears to be safe in children and young adults [10–12], although the occurrence of meningitis after vaccination with Mosquirix is still under evaluation [13], and narcolepsy has been observed following the use of Pandemrix [14–16].

The use of adjuvant in older adults may present different safety challenges, however, compared to their use in younger adults or children. In the light of the expected increased use of adjuvants in this age group, we decided to conduct a review of the combined observations of the use of adjuvants in the older adult population.

In this study, we systematically review the cumulative evidence on the safety of the newly adjuvanted vaccines in older adults and perform meta-analyses using data from published clinical trials. In particular, we perform meta-analyses for Serious Adverse Events (SAEs), local and general solicited AEs, and unsolicited AEs, by group of adjuvants and all adjuvants combined.

2. Methods

2.1. Data sources

We searched Medline (January 1st, 1995 to September 11th, 2017) for clinical trials including any of the new adjuvant systems. Additional relevant trials described in the selected publications were also extracted.

2.2. Study selection

Eligibility criteria for studies to be included in the meta-analysis were as follows: (1) randomized controlled trial (RCT); (2) study on the safety of vaccines using the adjuvant systems AS01, AS02, AS03, or MF59; (3) including older adults (i.e., reporting separately on those 50 years and older); and (4) reporting the safety of both the adjuvanted group and a control group.

The bivalent human papillomavirus (HPV) vaccine Cervarix and the hepatitis B vaccine Fendrix, both containing AS04, have been studied in adults, but not in the elderly. Therefore, we have not included AS04 in this review.

A literature search was performed in PubMed for the adjuvant-systems with the following search terms: (“vaccines”[MeSH Terms] OR “vaccines”[All Fields] OR “vaccine”[All Fields]) AND (“adjuvants, immunologic”[Pharmacological Action] OR “adjuvant”[All Fields] OR (“adjuvants”[All Fields] AND “immunologic” [All Fields])) AND ((“aged”[MeSH Terms] OR “aged”[All Fields] OR “elderly”[All Fields]) OR geriatric[All Fields]) AND “Clinical Trial” [All Fields] AND ((“1995/01/01″[PDAT] : ”2017/09/11″[PDAT]) AND English[lang]).

2.3. Outcomes

The following safety outcomes were investigated: (1) SAEs; (2) solicited local and general AEs; (3) unsolicited AEs and (4) potentially immune-mediated diseases (pIMDs). SAEs were monitored for the whole duration of the trial (ranging from 90 days to 42 months), solicited AEs mostly up to 1 week, and unsolicited AEs generally 3–4 weeks after each dose. For SAEs, solicited AEs, and unsolicited AEs, we performed meta-analyses by groups of adjuvant systems and across all adjuvant systems. Given their similar

Table 1
Clinical trials included in the meta-analysis on the safety of newly adjuvanted vaccines.

Study [ref no.]	Phase	Year	Country	Study population	NR. Subjects	Adjuvant	Vaccine	Control
Leroux-Roels 2012 [8]	2	2007–2008	Belgium	50–70	135	AS01b	HZ/su	OKA/HZ/su+OKA
Chlibek 2013 [9]	2	2009–2010-	CZ/ES/USA	60+	410	AS01b/AS01E	HZ/su	NA-HZ/su placebo
Chlibek 2014 [10]	2	2007–2011	CZ/DE/NL/SE	60+	715	AS01b	HZ/su	placebo
Lal 2015 [11]	3	2010–2014	World-wide	50+	15,411	AS01b	HZ/su	placebo
Cunningham 2016 [12]	3	2010–2015	World-wide	70+	14,816	AS01b	HZ/su	placebo
Leroux-Roels 2015 [13]	2	2004–2007	Belgium	65+	150	AS02v	PhtD	Alum-PhtD/23PPV
Pauksens 2014 [14]	1	2008–2009	Sweden	65–85	167	AS02v	PhtD/PCV8	Alum-PhtD/Alum-PCV8/23PPV
Rumke 2008 [15]	3	2006	Europe	60+	538	AS03	H5N1	Seasonal TIV
Heijmans 2011 [16]	2	2006–2008	Italy/Belgium	61+	437	AS03	H5N1	NA-H5N1
Gillard 2014 [17]	2	2006–2009	Italy/Belgium	60+	345	AS03	H5N1	H5N1
Langley 2011 [18]	3	2008–2009	North America	65+	1489	AS03	H5N1	placebo
McElhaney 2013 [19]	3	2008–2010	World-wide	65+	43,695	AS03	Seasonal TIV	Seasonal TIV
Ferguson 2012 [20]	2	2009–2010	USA/CA	61–90	681	AS03	H1N1	NA-H1Ni1
Yang 2013 [21]	3	2009–2011	USA/CA	65+	961	AS03	H1N1	NA-H1N1
Minutello 1999 [22]	2	1992–1994	Italy	65+	92	MF59	Seasonal TIV	Seasonal TIV
De Donato 1999 [23]		1993–1995	Italy	64–87	211	MF59	Seasonal TIV	Seasonal TIV
Gasparini 2001 [24]	3	1994–1995	Italy	65+	308	MF59	Seasonal TIV	Seasonal TIV
Squarcione 2003 [25]	4	1998–1999	Italy	65+	2150	MF59	Seasonal TIV	Seasonal TIV
Ruf 2004 [26]	3	2002–2003	Germany	60+	827	MF59	Seasonal TIV	Seasonal TIV
Li 2008 [27]	3	2006	China	60+	600	MF59	Seasonal TIV	Seasonal TIV
Della Cioppa 2012 [28]		2008–2009	PL/BE/DE	65+	357	MF59	Seasonal TIV	Seasonal TIV
Frey 2014 [29]	3	2010–2011	CO/PA/PHI/USA	65+	7109	MF59	Seasonal TIV	Seasonal TIV
Seo 2014 [30]	3	2011	Korea	65+	224	MF59	Seasonal TIV	Seasonal TIV
Scheifele 2013 [31]	4	2011–2012	Canada	65+	608	MF59	Seasonal TIV	Seasonal TIV
Song 2015 [32]	4	2013	Korea	65+	224	MF59	Seasonal TIV	PPV23
Song 2017 [33]		2014–2015	Korea	60+	1149	MF59	Seasonal TIV	PCV13

Countries: Be – Belgium; Ca – Canada; Co – Colombia; Cz – Czech Republic; De – Germany; Es – Spain; Nl – the Netherlands; Pa – Panama; Phi – Philippines; Pl – Poland; Se – Sweden; USA – United States of America.
Vaccines: HZ/su – herpes zoster subunit; NA – non-adjuvanted; OKA – varicella vaccine; PCV – pneumococcal conjugate vaccine; PhtD - Streptococcus pneumoniae vaccine; PPV – pneumococcal polysaccharide vaccine.

Please cite this article in press as: Baay M et al. A systematic review and meta-analysis on the safety of newly adjuvanted vaccines among older adults. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.06.004