International Journal of Cardiology 287 (2019) 118–119

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Editorial

Statin therapy for Takayasu Arteritis

Fulvio Salvo [a,*], Stefano Franchini [b]

[a] Azienda USL-IRCCS di Reggio Emilia, via Amendola 2, 42122 Reggio Emilia, Italy
[b] Ospedale San Raffaele, via Olgettina 60, 20132 Milano, Italy

ARTICLE INFO

Article history:
Received 22 March 2019
Received in revised form 1 April 2019
Accepted 8 April 2019
Available online 11 April 2019

First marketed >30 years ago, statins quickly became a therapeutic cornerstone in coronary artery disease primary and secondary prevention. Statins exert their low density lipoprotein-cholesterol lowering effect through inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the L-mevalonate pathway. During the last several years, knowledge on statins pharmacologic properties has constantly expanded, unveiling a surprisingly wide array of metabolic interactions which accounts, at least in part, for their complex biologic effects *in vivo* [1]. These so-called pleiotropic effects are mediated in part by inhibition of protein isoprenylation and are largely independent from their cholesterol lowering properties. Decreased (iso)prenylation reduces membrane anchoring and protein interaction of small guanosine triphosphate hydroxylases (GTPase) such as Rho and Ras, which regulate different crucial processes including cell proliferation, differentiation, migration, and apoptosis. Moreover, new evidences are accumulating to support mevalonate-indipendent effects through the interaction with different intracellular proteins, leading to modifications in gene expression and signal transduction. This complex network of actions, far from being completely understood, modulates the immune response at multiple levels and may account for the beneficial cardiovascular effect of statins, which could not be explained solely by cholesterol reduction.

Statins immunomodulatory properties have attracted the attention of researchers on their possible role in immune-mediated diseases. Statin therapy has been tested in many different diseases with different and somehow conflicting results. In Rheumatoid Arthritis for example a recent meta-analysis of the available studies showed that statin therapy may reduce disease activity and improve symptoms control by suppressing inflammatory response [2].

Despite undeniable advances in recent years, management of Takayasu Arteritis (TA) remains challenging. Steroid therapy is still the main option during the induction phase, but it fails to provide long term benefits and bears an unacceptably high rate of adverse events. Biologic agents, such as Tumor Necrosis Factor (TNF)-inhibitors, anti-interleukin (IL)-6 tocilizumab, and abatacept act through an efficient blockage of a specific arm of the immune response. Pooled data from a recent meta-analysis showed that overall biologic agents are associated with a similar response rate compared to classic disease modifying agents, but with a longer event-free survival [3]. Significant adverse events were more common with biologics and were mainly infections. However, the two randomized controlled trials with tocilizumab and abatacept both failed to meet their primary endpoints, respectively time-to-relapse and relapse-free survival [4,5]. With this background, it is evident the need for new therapies that can provide additional benefits on the course of the disease, without further increasing the risk of infectious adverse events.

In the article published on this journal, Kwon and co-authors investigated the potential effect of statin therapy on relapse rate in patients with TA [6]. This study suffers of course from the common limitations of retrospective observational studies on rare diseases, but it provides very valuable information, given its rigorous approach and the wise use of statistical analysis. They explored factors associated with relapses in their cohort of 74 Korean patients with newly diagnosed TA, followed for a median of 35.8 months at a single center. Among the other variables, patients with concomitant statin therapy experienced a significantly lower number of relapses compared to those not receiving statins (32.5% *vs* 67.6%, p 0.003). This result was confirmed in the multivariate analysis, where statin use was inversely associated with the risk of relapse, with an adjusted hazard ratio of 0.260 (p 0.001).

Exploring the possible immunologic explanation for this result is intriguing. The present knowledge about the pathophysiology of TA suggests that the primary inflammatory focus of this vasculitis is located in the vasa vasorum and at medio-adventitial junction [7]. However the experimental evidence regarding the anti-inflammatory proprieties of statins is mainly focused on their effect on the endothelial inflammatory response [8]. Nonetheless, as suggested by the Authors, statins seem to exert a systemic inhibitory effect on cell-mediated immunity, by reducing the secretion of IL-2, IL-12, and IL-17, and, thus, hampering both Th1 and Th17 responses [1], which are believed to play a major role in the pathogenesis of large-vessel vasculitides [8]. However, there are other pathways that could be involved in the protective effect of statins in TA patients, suggested by this study. Statins inhibit interferon-γ-induced MHC-II expression and subsequent T-cell activation [8], a crucial step sustaining granuloma formation typical of TA

DOI of original article: https://doi.org/10.1016/j.ijcard.2019.02.046.
* Corresponding author.
E-mail addresses: salvofulvio@hotmail.com (F. Salvo), franchini.stefano@hsr.it (S. Franchini).

https://doi.org/10.1016/j.ijcard.2019.04.024

Table 1
Selection of studies evaluating the effect of specific treatments on relapse rate in Takayasu Arteritis.

Drug	Study	Study Design	Patients		Country	Concomitant therapy	Median FU (months)	Rate of relapses	
Present study									
Statins	Kwon et al. Int J Cardiol 2019 [7]	Retrospective	74	40 Statins 34 No Statins	Korea	CS, MTX, AZA	35.8	Statins 13/40 (32.5%) No Statins 23/34 (67.6%)	p 0.003
Double-blind randomized controlled trials									
Tocilizumab	Nakaoka et al. Ann Rheum Dis 2018 [5]	DB RCT	36	18 TCZ 18 PCB	Japan	CS (tapering as per study protocol)	11	TCZ 8/18 (44%) PCB 11/18 (61%)	p 0.5
Abatacept	Langford et al. Arthritis Rheumatol 2017 [6]	DB RCT	34 (All received ABA + CS for 12 weeks)	Then randomized: 11 ABA 15 PCB 8 Withdrawn	USA	CS (tapering as per study protocol)	12	ABA 8/11 (73%) PCB 10/15 (67%)	$p \approx 1$
Restrospective studies and case series									
TNF-i	Schmidt et al. Arthritis Care Res 2012 [S-1]	Retrospective	20	17 IFX 2 ADA 1 ETN	USA	14 IFX/MTX; 2 IFX/AZA; 1 IFX MT; 2 ADA MT; 1 ETN MT	54	6/18 patients who achieved remission (33%) 2 patients did not achieve remission	
TNF-i	Molloy et al. Ann Rheum Dis 2008 [S-2]	Retrospective	25	21 IFX 9 ETN (5 switched to IFX)	USA	CS, IS	28	12/18 patients who achieved remission in IFX (67%), but only 2 "major relapses" 3/6 who achieved remission in ETN (50%), but only 2 "major relapses"	
Certolizumab	Novikov et al. Rheumatology (Oxford) 2018 [S-3]	Case series	10 CTP		Russia, Turkey	CS, MTX	10	1/8 patients with FU > 3 months (12%)	
Rituximab	Pazzola et al. Rheumatology (Oxford) 2017 [S-4]	Retrospective	7 RTX		Italy, France	CS	24	1/3 patients who achieved remission (33%) 4 patients did not achieve remission	

See Supplementary Material for additional References. CS: corticosteroids; MTX: methotrexate; AZA: azathioprine; TCZ: tocilizumab; ABA; abatacept; TNF-i: Tumor Necrosis Factor-inhibitors; IFX: infliximab; ADA: adalimumab; ETN: etanercept; CTP: certolizumab pegol; RTX: rituximab; IS: immunosuppressant; DB RCT: double-blind randomized controlled trials; MT: monotherapy; PCB: placebo.

[7]. IL-6 plays an important role in sustaining vascular wall damage in TA. In fact, this cytokine is secreted by activated macrophages and T lymphocytes and stimulates the production of matrix metalloproteinases from infiltrating mononuclear cells and smooth muscle cells of the arterial wall [7]. Statins have been shown to inhibit cytokine-stimulated expression of CD40, whose engagement by its ligand (CD154) on antigen-presenting cells is essential in inducing expression of cell adhesion molecules, metalloproteinases and chemokines, and other pro-inflammatory cytokines [8].

On the basis of such speculations and opting for a pragmatic approach, leading experts in the field of vasculitis have already introduced statin therapy for TA patients in their clinical practice in the last decade [9]. Moreover, a comparison of the effect of statins on TA relapse rate with other treatments is hampered by the marked heterogeneity of the studies currently available in the literature (in term of population, patient selection, measured outcomes, and treatment regimens) and by the low number of randomized placebo-controlled studies in this field. Anyway, an approximate idea of the impact of statin therapy on relapse rate of TA is summarized in Table 1.

The study by Kwon and colleagues represents the first objective evidence of a clinical benefit ascribable to statins for these patients, and, certainly, such preliminary findings are worth pursuing. Larger multicentric randomized controlled trials focused on the efficacy of statins in modifying the course of TA are clearly needed to confirm the results provided by this retrospective study. Hopefully, they could also represent a valuable occasion for a deeper understanding of both the pathogenesis of TA and the systemic immunomodulatory effects of statins. An opportunity to move from speculation to experimental evidence.

The authors did not receive any specific grant.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.024.

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