Neurosurgical Review (2022) 45:395–403
https://doi.org/10.1007/s10143-021-01628-9

REVIEW

Preclinical and clinical role of interleukin-6 in the development of delayed cerebral vasospasm and neuronal cell death after subarachnoid hemorrhage: towards a potential target therapy?

Davide Marco Croci[1,2,3] · Sivani Sivanrupan[2] · Stefan Wanderer[2,3] · Guilherme J. Agnoletto[1] · Alessio Chiappini[4] · Basil E. Grüter[2,3] · Lukas Andereggen[2,3] · Luigi Mariani[4] · Philipp Taussky[1] · Serge Marbacher[2,3]

Received: 29 March 2021 / Revised: 13 July 2021 / Accepted: 16 August 2021 / Published online: 27 August 2021

Abstract

Delayed cerebral vasospasm (DCVS), early brain injury (EBI), and delayed cerebral ischemia (DCI) are devastating complications after aneurysmal subarachnoid hemorrhage (SAH). Interleukin (IL)-6 seems to be an important interleukin in the inflammatory response after SAH, and many studies describe a strong correlation between IL-6 and worse outcome. The aim of this study was to systematically review preclinical and clinical studies that evaluated systemic and cerebral IL-6 levels after SAH and their relation to DCVS, neuronal cell death, and DCI. We conducted two systematic literature searches using PubMed to identify preclinical and clinical studies evaluating the role of IL-6 after SAH. Suitable articles were selected based on predefined eligibility criteria following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A total of 61 and 30 preclinical and clinical articles, respectively, were included in the systematic reviews. Of the preclinical studies in which IL-6 was measured in cerebrospinal fluid (CSF), parenchyma, and systemically, 100%, 94.4%, and 81.3%, respectively, showed increased expression of IL-6 after SAH. Preclinical results were mirrored by clinical findings in which elevated levels of IL-6 in CSF and plasma were found after SAH, correlating with DCVS, DCI, and worse outcome. Only two preclinical studies analyzed the direct inhibition of IL-6, which resulted in reduced DCVS and neuronal cell death. IL-6 is a marker of intracranial inflammation and plays a role in the pathophysiology of DCVS and DCI after SAH in preclinical animal models and clinical studies. Its inhibition might have therapeutic potential to improve the outcome of SAH patients.

Keywords Interleukin-6 · Subarachnoid hemorrhage · Inflammation · Delayed cerebral ischemia · Vasospasm

Introduction

Delayed cerebral vasospasm (DCVS), early brain injury (EBI), and delayed cerebral ischemia (DCI) are potential devastating complications after aneurysmal subarachnoid hemorrhage (SAH). Despite recent advances in the treatment of SAH, neurological outcomes remain poor, and new therapeutic approaches for preventing and treating DCVS and DCI are highly warranted [1–3]. Randomized controlled trials using clazosentan, an ET-1 receptor antagonist, showed a decrease of DCVS but no improvement in the outcome of SAH [4, 5]. This led the scientific community to reevaluate factors other than DCVS that might cause poor clinical outcome after SAH. Inflammation after SAH has been revealed to be an important contributor leading to DCVS, DCI, and worse outcome. Various inflammatory cytokines and interleukins have been described as initiators of the inflammation cascade after blood products are spilled in the

Davide Marco Croci and Sivani Sivanrupan are authors contributed equally to this work

✉ Davide Marco Croci
neurosurgery@ksa.ch; crocidav@gmail.com

[1] Department of Neurosurgery, Clinical Neurosciences Center, University of Utah, 175 N Medical Drive East, Salt Lake City, UT 84132, USA

[2] Cerebrovascular Research Group, Department of BioMedical Research, University of Bern, Bern, Switzerland

[3] Department of Neurosurgery, Kantonsspital Aarau, c/o NeuroResearch Office, Tellstrasse 1, 5001 Aarau, Switzerland

[4] Department of Neurosurgery, University Hospital Basel, Basel, Switzerland

subarachnoid space after aneurysm rupture that play a fundamental role in EBI [6–9]. Preclinical and clinical studies revealed that interleukin (IL)-6 seems to be one of the interleukins involved in the inflammatory response after SAH. Moreover, a growing body of clinical studies has described a strong correlation between IL-6 and worse outcome, corroborating previous findings described in preclinical animal studies where IL-6 was also showed to correlate with DCVS and neuronal cell death [6, 7, 9–12]. The aim of this study was to perform a systematic review of preclinical and clinical studies that evaluated systemic and cerebral IL-6 levels after SAH and their relation to DCVS, neuronal cell death, and DCI.

Material and methods

Two separate systematic literature searches in the Medline/PubMed database were conducted in January 2021 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [13]. In both searches, two investigators (DC and SS) independently screened the titles and abstracts and identified articles based on the predefined eligibility criteria following the PRISMA guidelines [13]. The final articles included were selected based on the full text of the eligible studies. Discrepancies in the study selection were discussed between the authors DC and SS until a consensus was reached. Institutional review board approval was not required for this review of published data.

First, a literature search was performed to identify preclinical studies investigating the role of IL-6 in the pathophysiology of DCVS and DCI after SAH. The keywords used were "interleukin-6" and "subarachnoid hemorrhage" using the Boolean operator (AND). The search was restricted to animals by using the MEDLINE PubMed limit "animals." Eligible studies were in vivo experimental mice, rat, rabbit, cat, dog, pig, goat, and nonhuman primate studies in which IL-6 was investigated in cerebrospinal fluid (CSF), brain parenchyma, brain vessels, and plasma after SAH. Studies on extracranial vessels, organs other than the brain, or in vitro were excluded. From the eligible preclinical articles, we extracted publications details (i.e., authors, journal, date), animal species, SAH induction techniques, and outcome measures (DCVS, DCI, direct vessel observation, neuronal cell death and degeneration, blood–brain barrier disruption, contractile vessel response).

The second literature search was performed to identify clinical studies investigating IL-6 and occurrence of DCVS and DCI after SAH and assessing clinical outcome. The keywords used were "interleukin-6" and "subarachnoid hemorrhage" using the Boolean operator (AND). The search was restricted to humans using the MEDLINE PubMed limit "humans." The inclusion criteria were all studies evaluating plasma and CSF levels of IL-6 in relation to DCVS, DCI, and patients' outcome. Studies investigating possible therapeutics approaches other than direct inhibition of IL-6, and relations to infections and hydrocephalus or systemic complications were excluded. From the eligible clinical articles, we extracted publications details (i.e., authors, journal, date), number of patients, IL-6 measurement methods (CSF, plasma), and primary and secondary outcome parameters (DCVS, DCI, clinical outcome).

Results

Animal studies

After duplicates were removed, a total of 61 articles were found that analyzed the effect of IL-6 in animal models (Supplementary Table 1). The initial electronic search yielded 98 potential studies. Of these, 35 articles were excluded after reviewing the title and abstract. The remaining 63 articles underwent full-text analysis. Of those, 2 studies were excluded per the predefined eligibility criteria (Fig. 1). Of the final 61 articles, 44 studies were performed on rats (72.1%), 9 on mice (14.8%), 5 on rabbits (8.2%), and 3 on dogs (4.9%). In rats, the most common SAH model used was the cisterna magna injection model in 19 studies (43.2%), followed by the endovascular perforation model in 18 studies (40.9%) and the prechiasmatic blood injection model in 7 studies (15.9%). In mice, the endovascular perforation model was used in 7 studies (77.8%) and the prechiasmatic blood injection model in 2 studies (22.2%). In rabbits, 3 studies (60%) used the closed cranium extracranial-intracranial shunt model and 2 studies (40%) the double hemorrhage model. In dogs, the models used were the cisterna magna blood injection model in 2 studies (66.7%) and the endovascular perforation model in one study (33.3%) (Fig. 2).

Nearly three-quarters of the studies (45, 73.7%) addressed the research question of EBI, whereas 24 studies (39.3%) examined DCVS. Twelve studies (19.6%) addressed both EBI and DCVS, and four studies (6.6%) did not focus their research question on DCVS and EBI, instead examining only interleukin concentrations.

Overall, IL-6 was measured in brain parenchyma in 36 studies (59%), in plasma/serum in 16 studies (26.2%), in CSF in 14 studies (22.9%), and in cerebral arteries and endothelial cells in 7 studies (11.4%) (some studies measured IL-6 in multiple locations) (Table 1). Of the 36 studies in which IL-6 was measured in brain parenchyma, 34 (94.4%) found an increased expression of IL-6 in parenchyma after SAH. In all the studies in which IL-6 was measured in CSF, an increase of IL-6 expression after SAH was noted. Of the 16 studies in which IL-6 was measured in plasma/serum, 13 (81.3%) showed an increase of IL-6 after

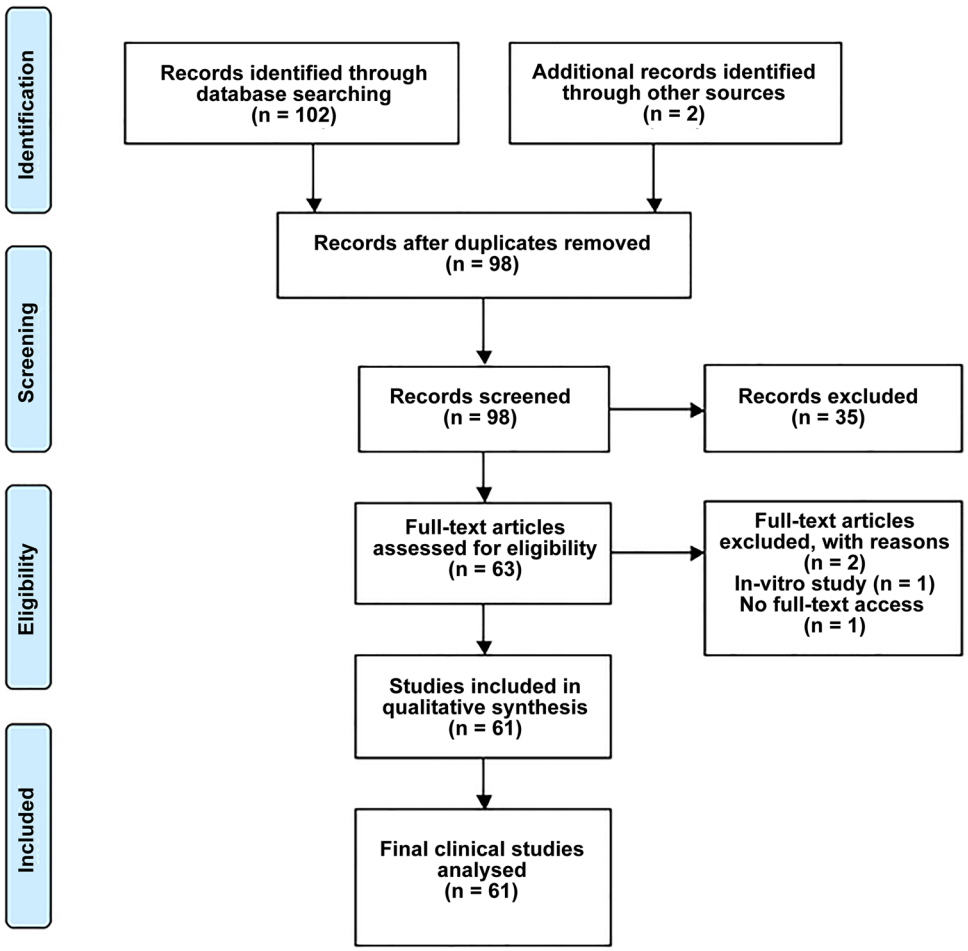

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for preclinical animal studies selection

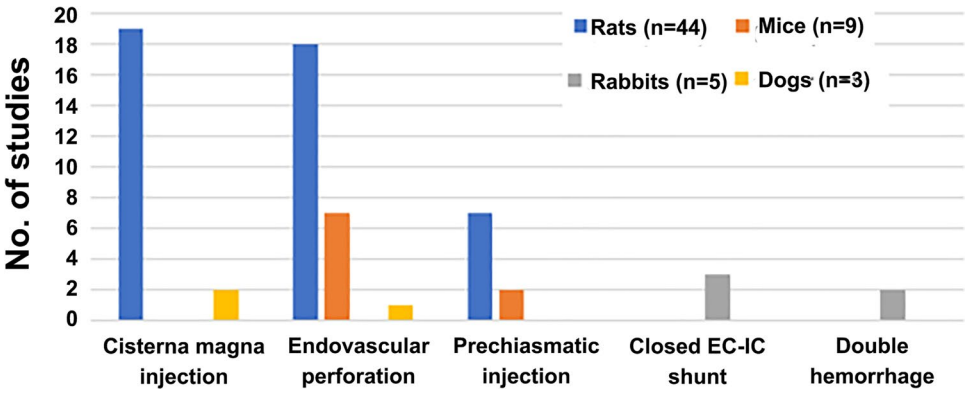

Fig. 2 Subarachnoid hemorrhage model used in various animal species studies

Table 1 Animal and human studies measuring interleukin-6 in cerebrospinal fluid, plasma/serum, parenchyma, and the cerebral vasculature

IL-6 measurement	Animal ($n=61$)		Human ($n=30$)	
	Number (%) of studies	**Number (%) of studies showing increase in IL-6**	**Number (%) of studies**	**Number (%) of studies showing increase in IL-6**
Cerebrospinal fluid (%)	14 (22.9)	14 (100)	17 (56.7)	17 (100)
Plasma/serum (%)	16 (26.2)	13 (81.3)	23 (76.7)	23 (100)
Parenchyma (%)	36 (59)	34 (94.4)	-	-
Cerebral vasculature (%)	7 (11.4)	7 (100)	-	-

SAH induction. An increase of IL-6 expression in cerebral vasculature after SAH was described in all of the studies where IL-6 was measured in the cerebral vasculature. Overall, 52 studies (85.2%) aimed their research on a possible therapeutic substance after SAH and their effect on IL-6 as well (Supplementary Table 1); however, only two studies (3.2%) analyzed the direct inhibition of IL-6 through a receptor antagonist. The first of these analyzed the effect of a direct IL-6 antagonist in vivo with the IL-6 receptor antagonist tocilizumab, which resulted in decreased DCVS, neuronal cell death, and microclot formation [14]. In the second study, an IL-6 antagonist was applied only vitro, with blockade of the membranous IL-6 receptor with a goat polyclonal IL-6R-neutralizing antibody (IL-6R nAb), and resulted in an inhibition of brain endothelial cell barrier disruption after SAH [15].

Human studies

After duplicates were removed, a total of 30 articles were found that analyzed the effect of IL-6 in clinical studies (Supplementary Table 2). The initial electronic search yielded 105 potential studies. Of these, 25 articles were excluded after reviewing the title and abstract. The remaining 80 articles underwent full-text analysis. Of those, 50 studies were excluded per the predefined eligibility criteria (Fig. 3).

On average, 55.9 (7–179) patients were included per study, and 28 (93.3%) of the studies were prospective cohorts. In 17 studies (56.7%), IL-6 was measured in CSF; in 23 studies (76.7%), it was measured in plasma/serum; and in 10 studies (33.3%), it was measured in both (Table 1).

An increase of IL-6 after SAH was found in all of the studies where IL-6 was measured in CSF or plasma/serum, but the increased concentration of IL-6 was especially marked in CSF. In fact, in all 9 studies where IL-6 was measured in both CSF and plasma/serum, significantly higher values of IL-6 were demonstrated in CSF compared with plasma/serum.

Of the 13 studies where an association between DCVS and IL-6 concentrations in either CSF or plasma/serum was analyzed, 9 (69.2%) described a statistically significant association between IL-6 and DCVS, with an additional study showing a positive trend. On the other hand, of 15 studies (50%) where a possible correlation between IL-6 and the occurrence of delayed ischemic neurologic deficit (DIND)

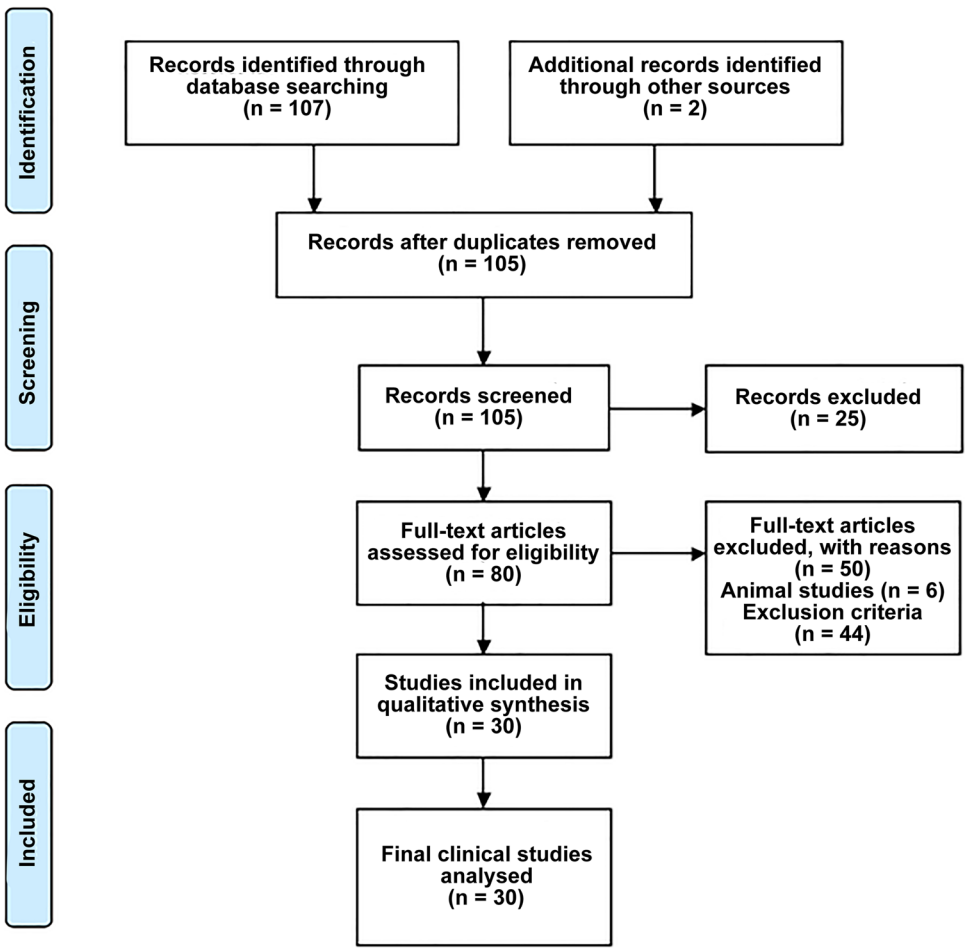

Fig. 3 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for human studies selection

and DCI was analyzed, 10 studies (66.6%) described a statistically significant association between IL-6 concentrations (either in CSF or plasma/serum) and DCI/DIND, with additional 2 studies (13.3%) showing a positive trend. Of 16 studies in which an association between IL-6 concentrations and outcome was analyzed, 12 studies (75%) showed that higher concentrations of IL-6 either in CSF or plasma/serum corresponded with worse patient outcome, with an additional study showing a trend of higher CSF IL-6 concentrations in patients with worse outcome. No studies analyzed any kind of direct inhibitor of IL-6 as therapeutic agent.

Discussion

In this systematic review, we identified 61 animal studies that evaluated the effects of IL-6 in SAH models. Nearly all of the studies in which IL-6 was measured in CSF and parenchyma—100% and 94.4%, respectively—showed increased expression of IL-6 after SAH induction. Moreover, an increased expression of IL-6 in plasma/serum was described in 81.3% of the studies. These results were mirrored in human studies. All clinical studies in which IL-6 was measured in CSF or plasma/serum demonstrated an increase of IL-6 after SAH. Both in animal models and in humans, IL-6 concentrations after SAH have been described to be significantly higher in CSF compared with plasma/serum, further illustrating that the main inflammatory reaction after SAH is mostly compartmentalized intracranially, as a response to the presence of blood in the subarachnoid space [16].

IL-6 in relation to DCVS and DCI

Osuka et al. [12] described an increase of IL-6 in CSF after SAH, which was considerably higher in patients experiencing DCVS. In the same study, they described that a single application of IL-6 in the CSF of dogs after SAH caused DCVS. Similar results were reported by our research group as well: we observed that the intrathecal application of IL-6 in rabbits led to an increased expression of the vasoconstrictor endothelin (ET)-1 and to DCVS [6].

The effect of IL-6 on vasoconstriction on arteries was demonstrated by Bowman et al. [17] in a rat femoral artery vasospasm model, where a significant increase of IL-6 was found in blood-exposed spastic arteries and the administration of a polyclonal antibody against IL-6 reduced vasospasm. Apoptotic damage to the endothelium and smooth muscle cells of cerebral arteries is known to be a factor in obstructing the physiologic vasoregulation and breaking down the blood–brain barrier after SAH [18–21]. In this context, IL-6 has been shown to be an important mediator in apoptosis, and barrier disruptive effects and inhibition of IL-6 attenuated vascular inflammation and endothelial barrier disruption of retinal endothelial cells [22]. Aihara et al. described higher mRNa expression of IL-6 in the endothelial wall of spastic basilar artery in dogs after SAH, a finding that was confirmed by other studies that showed a higher expression of IL-6 in endothelium of spastic cerebral arteries after SAH [23–26]. The role of IL-6 in endothelial damage and subsequently disruption of the blood–brain barrier has been described by Blecharz Lang et al. [15], who noted a significant overexpression of IL-6 and the IL-6 receptor (IL-6R) in the endothelium after SAH. Moreover, they showed that the in vitro inhibition of IL-6 with a polyclonal IL-6R neutralizing antibody led to an inhibition of brain endothelial cell barrier disruption through direct inference with the IL-6 signaling pathway. Although it seems unlikely that IL-6 induces DCVS directly, it is more likely that it works indirectly as a mediator by stimulating activation of CSF monocytes that in turn secrete ET-1 or as a result of its role in impairing cerebral autoregulation [7, 8, 27, 28].

The preclinical results were mirrored on clinical studies. In the early 1990s, studies described an upregulation of different inflammatory cytokines after SAH and correlated the upregulation with the occurrence of DCVS and worse clinical outcomes [7, 29–31]. In 1993, Mathiesen et al. [29] first described a marked increase of IL-6 in CSF (up to 300-fold higher than systemically) in a prospective cohort of SAH patients. Moreover, they noticed that mean CSF IL-6 concentrations were increased in patients with DCI. After this study, the role of inflammation and especially of IL-6 gained interest in the research field of EBI, DCVS, and DCI after SAH. During the next decades, more studies identified IL-6 as one of the most upregulated interleukins after SAH and named it a crucial player in the inflammation cascade after SAH (Fig. 4).

Several studies described the significant association between IL-6 and DCVS [7, 16, 32–38]. Similar to a preclinical study published by our group [7, 8], Fassbender et al. [7, 8] demonstrated a correlation between IL-6 and ET-1 in patients with SAH.

DCVS is not the only factor leading to poor outcome after SAH. In this context, DCI plays a relevant role as well. DCI is characterized by neuronal cell death and, even here, IL-6 has been shown to plays a role. Clinical studies have shown equivalent results to those from 10 animal studies that described a statistically significant association between IL-6 concentrations (either in CSF or plasma/serum) and DCI/DIND, with additional 2 studies showing a positive trend [7, 10, 12, 35, 38–42]. From previous rabbit studies, we know that a single intrathecal application of IL-6 in rabbits can lead to neuronal cell death [6]. After SAH, IL-6 seems to act as an intermediate that induces the aggregation of inflammatory cells in a lesion area, increasing the release of oxygen-free radicals from neutrophils and collaborating with TNF-α

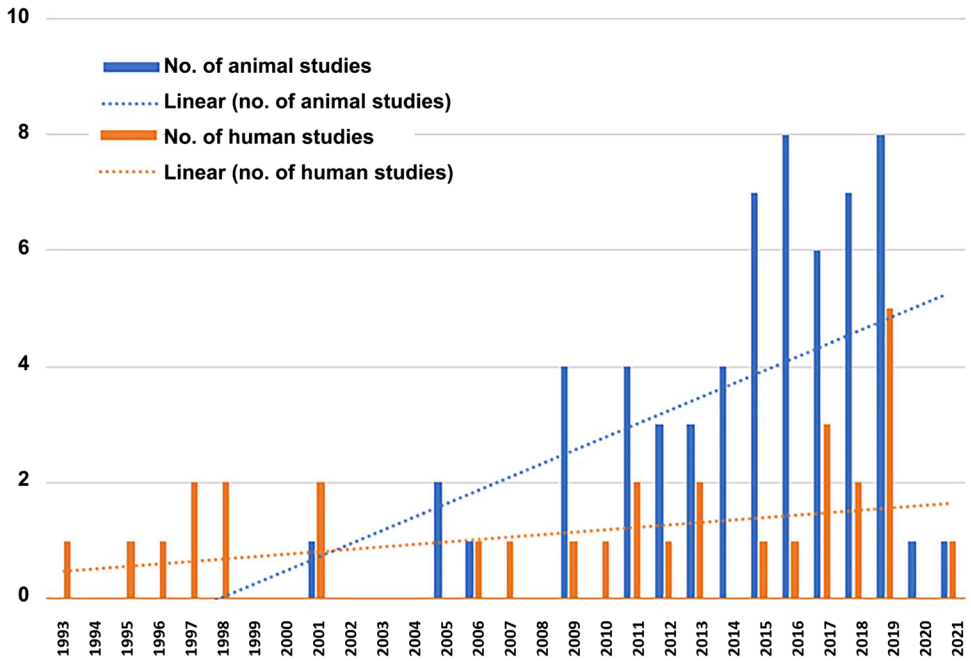

Fig. 4 Number of animal and human studies analyzing the role of interleukin-6 after subarachnoid hemorrhage published per year from 1993 to 2021

to promote neuronal cell apoptosis through calcium overload in the cells [43, 44].

IL-6 in relation to microclot formation

Differences in the time course and location of DCVS and DCI have questioned the cause-and-effect relationship: that is, clinically not all patients who develop DCVS have DCI, and not all patients with DCI have DCVS [45–49]. Microclot formation has been considered as a possible contributing factor for DCI, because of microvessel occlusion that leads to neuronal ischemia, degeneration, and apoptosis [48, 50, 51]. After aneurysmal rupture, blood products are spilled out within the subarachnoid space. The degradation and breakdown of red blood cells results in the deposition of methemoglobin, heme, and hemin, which lead to the activation of TLR4 and the subsequent initiation of the inflammatory cascade [52, 53]. Immunomodulatory cells such as microglia are activated and, together with endothelial cells, upregulate the secretion of IL-6, which is released into both the serum and cerebrospinal fluid after SAH [29, 54]. The expression of IL-6 has been noted to be increased in the cerebral arterial wall [55]. Different studies have described prothrombogenic actions of IL-6 [56–58]. Moreover, IL-6 together with TNF-α and IL-1 is known to induce tissue factor upregulation, which in turn promotes a procoagulant state among endothelial cells [59]. IL-6 inhibits the cleavage of ultralarge von Willebrand factor, resulting in platelet aggregation and adhesion of the vascular endothelium, thus possibly causing thrombosis in the microvessels [60]. These endothelial and hemostatic dysfunctions with development of microclots are highly involved in the pathophysiology of EBI and the development of DCI [14, 61, 62]. Different preclinical SAH models in mice and rabbits have confirmed microclot formations after SAH [14, 61, 63]. Human autopsy studies on SAH patients also demonstrated the presence of microclots and a correlation with location and severity of ischemia [48, 50, 51]. We previously demonstrated in a rabbit SAH model how the IL-6 receptor antagonist tocilizumab significantly reduced microclot formation, neuronal cell death, and DCVS [14].

Considering the poor outcome of SAH patients as a result of DCVS and DCI, new therapeutic approaches in treating and preventing DCVS and DCI are highly warranted. As we have seen, IL-6 is marker of neuroinflammation after SAH and seems to be relevant in the pathophysiology of DCVS and DCI. Therefore, it seems reasonable to develop new therapies against neuroinflammation to prevent the aggravation of EBI and improve outcome of patients with SAH. Given that animal models have shown that use of an IL-6 antagonist led to a decrease of DCVS, DCI, and microclot formation [14, 15, 17] and considering the availability of medications such as the IL-6 receptor antagonist tocilizumab, which is widely used in the treatment of rheumatoid arthritis [64–66] and was recently used in clinical studies for treatment of patients affected by COVID-19 [67–69], new doors have opened for possible future clinical trials using an IL-6 receptor antagonist in an effort to decrease DCVS and DCI after SAH to improve patient outcomes.

Conclusions

IL-6 is a marker of intracranial inflammation and seems to play an important role in the pathophysiology of DCVS and DCI after SAH in preclinical and clinical studies. Its inhibition might be a possible therapeutic approach to improve the outcome of SAH patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10143-021-01628-9.

Author contribution Conception and design: Croci, Sivanrupan, Marbacher. Drafting the article: Croci, Sivanrupan, Agnoletto, Chiappini, Wanderer, Grüter, Marbacher. Statistical analysis and interpretation of data: Croci, Wanderer, Andereggen, Marbacher. Critically revising the article: Andereggen, Marbacher, Taussky, Mariani. Administrative support: Grüter, Marbacher.

Availability of data and material The authors declare that all supporting data are available within the article and its online supplementary files.

Code availability Not applicable.

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate Not applicable.

Consent to publish Not applicable.

Competing interests The authors declare no competing interests.

References

1. Kassell NF, Sasaki T, Colohan AR et al (1985) Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. Stroke 16:562–572. https://doi.org/10.1161/01.str.16.4.562
2. Konczalla J, Kashefiolasl S, Brawanski N et al (2017) Cerebral vasospasm-dependent and cerebral vasospasm-independent cerebral infarctions predict outcome after nonaneurysmal subarachnoid hemorrhage: a single-center series with 250 patients. World Neurosurg 106:861-869.e864. https://doi.org/10.1016/j.wneu.2017.07.017
3. Neifert SN, Chapman EK, Martini ML et al (2021) Aneurysmal subarachnoid hemorrhage: the last decade. Transl Stroke Res 12:428–446. https://doi.org/10.1007/s12975-020-00867-0
4. Macdonald RL, Higashida RT, Keller E et al (2011) Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol 10:618–625. https://doi.org/10.1016/s1474-4422(11)70108-9
5. Macdonald RL, Higashida RT, Keller E et al (2012) Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling. Stroke 43:1463–1469. https://doi.org/10.1161/strokeaha.111.648980
6. Croci D, Nevzati E, Danura H et al (2019) The relationship between IL-6, ET-1 and cerebral vasospasm, in experimental rabbit subarachnoid hemorrhage. J Neurosurg Sci 63:245–250. https://doi.org/10.23736/s0390-5616.16.03876-5
7. Fassbender K, Hodapp B, Rossol S et al (2001) Inflammatory cytokines in subarachnoid haemorrhage: association with abnormal blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry 70:534–537. https://doi.org/10.1136/jnnp.70.4.534
8. Fassbender K, Hodapp B, Rossol S et al (2000) Endothelin-1 in subarachnoid hemorrhage: An acute-phase reactant produced by cerebrospinal fluid leukocytes. Stroke 31:2971–2975. https://doi.org/10.1161/01.str.31.12.2971
9. Niwa A, Osuka K, Nakura T et al (2016) Interleukin-6, MCP-1, IP-10, and MIG are sequentially expressed in cerebrospinal fluid after subarachnoid hemorrhage. J Neuroinflammation 13:217. https://doi.org/10.1186/s12974-016-0675-7
10. Gaetani P, Tartara F, Pignatti P et al (1998) Cisternal CSF levels of cytokines after subarachnoid hemorrhage. Neurol Res 20:337–342. https://doi.org/10.1080/01616412.1998.11740528
11 Muroi C, Hugelshofer M, Seule M et al (2013) Correlation among systemic inflammatory parameter, occurrence of delayed neurological deficits, and outcome after aneurysmal subarachnoid hemorrhage. Neurosurgery 72:367–375. https://doi.org/10.1227/NEU.0b013e31828048ce (**discussion 375**)
12. Osuka K, Suzuki Y, Tanazawa T et al (1998) Interleukin-6 and development of vasospasm after subarachnoid haemorrhage. Acta Neurochir (Wien) 140:943–951. https://doi.org/10.1007/s007010050197
13. Moher D, Liberati A, Tetzlaff J et al (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 8:336–341. https://doi.org/10.1016/j.ijsu.2010.02.007
14. Croci DM, Wanderer S, Strange F et al (2021) Tocilizumab reduces vasospasms, neuronal cell death, and microclot formation in a rabbit model of subarachnoid hemorrhage. Transl Stroke Res. https://doi.org/10.1007/s12975-020-00880-3
15. Blecharz-Lang KG, Wagner J, Fries A et al (2018) Interleukin 6-mediated endothelial barrier disturbances can be attenuated by blockade of the IL6 Receptor expressed in brain microvascular endothelial cells. Transl Stroke Res 9:631–642. https://doi.org/10.1007/s12975-018-0614-2
16. Al-Tamimi YZ, Bhargava D, Orsi NM et al (2019) Compartmentalisation of the inflammatory response following aneurysmal subarachnoid haemorrhage. Cytokine 123:154778. https://doi.org/10.1016/j.cyto.2019.154778
17 Bowman G, Dixit S, Bonneau RH et al (2004) Neutralizing antibody against interleukin-6 attenuates posthemorrhagic vasospasm in the rat femoral artery model. Neurosurgery 54:719–725. https://doi.org/10.1227/01.neu.0000108981.73153.6e (**discussion 725-726**)
18. Choy JC, Granville DJ, Hunt DW et al (2001) Endothelial cell apoptosis: biochemical characteristics and potential implications for atherosclerosis. J Mol Cell Cardiol 33:1673–1690. https://doi.org/10.1006/jmcc.2001.1419
19. Friedrich V, Flores R, Sehba FA (2012) Cell death starts early after subarachnoid hemorrhage. Neurosci Lett 512:6–11. https://doi.org/10.1016/j.neulet.2012.01.036
20. Zhou C, Yamaguchi M, Colohan AR et al (2005) Role of p53 and apoptosis in cerebral vasospasm after experimental subarachnoid hemorrhage. J Cereb Blood Flow Metab 25:572–582. https://doi.org/10.1038/sj.jcbfm.9600069
21. Zhou C, Yamaguchi M, Kusaka G et al (2004) Caspase inhibitors prevent endothelial apoptosis and cerebral vasospasm in dog model of experimental subarachnoid hemorrhage. J Cereb

Blood Flow Metab 24:419–431. https://doi.org/10.1097/00004647-200404000-00007
22. Valle ML, Dworshak J, Sharma A et al (2019) Inhibition of interleukin-6 trans-signaling prevents inflammation and endothelial barrier disruption in retinal endothelial cells. Exp Eye Res 178:27–36. https://doi.org/10.1016/j.exer.2018.09.009
23. Aihara Y, Kasuya H, Onda H et al (2001) Quantitative analysis of gene expressions related to inflammation in canine spastic artery after subarachnoid hemorrhage. Stroke 32:212–217. https://doi.org/10.1161/01.str.32.1.212
24. Fang Q, Chen G, Zhu W et al (2009) Influence of melatonin on cerebrovascular proinflammatory mediators expression and oxidative stress following subarachnoid hemorrhage in rabbits. Mediators Inflamm 2009:426346. https://doi.org/10.1155/2009/426346
25. Lin C, Zhao Y, Wan G et al (2016) Effects of simvastatin and taurine on delayed cerebral vasospasm following subarachnoid hemorrhage in rabbits. Exp Ther Med 11:1355–1360. https://doi.org/10.3892/etm.2016.3082
26. Zhang J, Xu X, Zhou D et al (2015) Possible role of Raf-1 kinase in the development of cerebral vasospasm and early brain injury after experimental subarachnoid hemorrhage in rats. Mol Neurobiol 52:1527–1539. https://doi.org/10.1007/s12035-014-8939-7
27. Fujimori A, Yanagisawa M, Saito A et al (1990) Endothelin in plasma and cerebrospinal fluid of patients with subarachnoid haemorrhage. Lancet 336:633. https://doi.org/10.1016/0140-6736(90)93432-o
28. Hino A, Weir BK, Macdonald RL et al (1995) Prospective, randomized, double-blind trial of BQ-123 and bosentan for prevention of vasospasm following subarachnoid hemorrhage in monkeys. J Neurosurg 83:503–509. https://doi.org/10.3171/jns.1995.83.3.0503
29. Mathiesen T, Andersson B, Loftenius A et al (1993) Increased interleukin-6 levels in cerebrospinal fluid following subarachnoid hemorrhage. J Neurosurg 78:562–567. https://doi.org/10.3171/jns.1993.78.4.0562
30. Mathiesen T, Edner G, Ulfarsson E et al (1997) Cerebrospinal fluid interleukin-1 receptor antagonist and tumor necrosis factor—α following subarachnoid hemorrhage. J Neurosurgery 87:215. https://doi.org/10.3171/jns.1997.87.2.0215
31. Mathiesen T, Lefvert AK (1996) Cerebrospinal fluid and blood lymphocyte subpopulations following subarachnoid haemorrhage. Br J Neurosurg 10:89–92. https://doi.org/10.1080/02688699650040584
32. Chamling B, Gross S, Stoffel-Wagner B et al (2017) Early diagnosis of delayed cerebral ischemia: possible relevance for inflammatory biomarkers in routine clinical practice? World Neurosurg 104:152–157. https://doi.org/10.1016/j.wneu.2017.05.021
33. Chaudhry SR, Stoffel-Wagner B, Kinfe TM et al (2017) Elevated systemic IL-6 Levels in patients with aneurysmal subarachnoid hemorrhage is an unspecific marker for post-SAH complications. Int J Mol Sci 18:2580. https://doi.org/10.3390/ijms18122580
34. Kwon KY, Jeon BC (2001) Cytokine levels in cerebrospinal fluid and delayed ischemic deficits in patients with aneurysmal subarachnoid hemorrhage. J Korean Med Sci 16:774–780. https://doi.org/10.3346/jkms.2001.16.6.774
35. Muroi C, Bellut D, Coluccia D et al (2011) Systemic interleukin-6 concentrations in patients with perimesencephalic non-aneurysmal subarachnoid hemorrhage. J Clin Neurosci 18:1626–1629. https://doi.org/10.1016/j.jocn.2011.03.022
36. Muroi C, Seule M, Sikorski C et al (2013) Systemic interleukin-6 levels reflect illness course and prognosis of patients with spontaneous nonaneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl 115:77–80. https://doi.org/10.1007/978-3-7091-1192-5_17
37. Sarrafzadeh A, Schlenk F, Gericke C et al (2010) Relevance of cerebral interleukin-6 after aneurysmal subarachnoid hemorrhage. Neurocrit Care 13:339–346. https://doi.org/10.1007/s12028-010-9432-4
38. Vlachogiannis P, Hillered L, Khalil F et al (2019) Interleukin-6 Levels in cerebrospinal fluid and plasma in patients with severe spontaneous subarachnoid hemorrhage. World Neurosurg 122:e612–e618. https://doi.org/10.1016/j.wneu.2018.10.113
39. Chaudhry WN, Concepción-Acevedo J, Park T et al (2017) Synergy and order effects of antibiotics and phages in killing Pseudomonas aeruginosa biofilms. PLoS ONE 12:e0168615. https://doi.org/10.1371/journal.pone.0168615
40. Ni W, Gu YX, Song DL et al (2011) The relationship between IL-6 in CSF and occurrence of vasospasm after subarachnoid hemorrhage. Acta Neurochir Suppl 110:203–208. https://doi.org/10.1007/978-3-7091-0353-1_35
41. Schneider UC, Davids AM, Brandenburg S et al (2015) Microglia inflict delayed brain injury after subarachnoid hemorrhage. Acta Neuropathol 130:215–231. https://doi.org/10.1007/s00401-015-1440-1
42 Schoch B, Regel JP, Wichert M et al (2007) Analysis of intrathecal interleukin-6 as a potential predictive factor for vasospasm in subarachnoid hemorrhage. Neurosurgery 60:828–836. https://doi.org/10.1227/01.Neu.0000255440.21495.80 (**discussion 828-836**)
43. Aly H, Khashaba MT, El-Ayouty M et al (2006) IL-1beta, IL-6 and TNF-alpha and outcomes of neonatal hypoxic ischemic encephalopathy. Brain Dev 28:178–182. https://doi.org/10.1016/j.braindev.2005.06.006
44. Li SJ, Liu W, Wang JL et al (2014) The role of TNF-α, IL-6, IL-10, and GDNF in neuronal apoptosis in neonatal rat with hypoxic-ischemic encephalopathy. Eur Rev Med Pharmacol Sci 18:905–909
45. Macdonald RL, Pluta RM, Zhang JH (2007) Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution. Nat Clin Pract Neurol 3:256–263. https://doi.org/10.1038/ncpneuro0490
46. Nolan CP, Macdonald RL (2006) Can angiographic vasospasm be used as a surrogate marker in evaluating therapeutic interventions for cerebral vasospasm? Neurosurg Focus 21:E1. https://doi.org/10.3171/foc.2006.21.3.1
47. Rowe J, Renowden S, Cadoux-Hudson T (1995) Screening for intracranial aneurysms. Short natural course makes screening impracticable. BMJ (Clinical research ed) 311:1227–1228. https://doi.org/10.1136/bmj.311.7014.1227b
48 Stein SC, Browne KD, Chen XH et al (2006) Thromboembolism and delayed cerebral ischemia after subarachnoid hemorrhage: an autopsy study. Neurosurgery 59:781–787. https://doi.org/10.1227/01.Neu.0000227519.27569.45 (**discussion 787-788**)
49. Treggiari MM, Walder B, Suter PM et al (2003) Systematic review of the prevention of delayed ischemic neurological deficits with hypertension, hypervolemia, and hemodilution therapy following subarachnoid hemorrhage. J Neurosurg 98:978–984. https://doi.org/10.3171/jns.2003.98.5.0978
50. Romano JG, Forteza AM, Concha M et al (2002) Detection of microemboli by transcranial Doppler ultrasonography in aneurysmal subarachnoid hemorrhage. Neurosurgery 50:1026–1030. https://doi.org/10.1097/00006123-200205000-00016 (**discussion 1030-1031**)
51. Romano JG, Rabinstein AA, Arheart KL et al (2008) Microemboli in aneurysmal subarachnoid hemorrhage. J Neuroimaging 18:396–401. https://doi.org/10.1111/j.1552-6569.2007.00215.x
52. Ascenzi P, Bocedi A, Visca P et al (2005) Hemoglobin and heme scavenging. IUBMB Life 57:749–759. https://doi.org/10.1080/15216540500380871
53. Pradilla G, Chaichana KL, Hoang S et al (2010) Inflammation and cerebral vasospasm after subarachnoid hemorrhage. Neurosurg Clin N Am 21:365–379. https://doi.org/10.1016/j.nec.2009.10.008

54. Kikuchi T, Okuda Y, Kaito N et al (1995) Cytokine production in cerebrospinal fluid after subarachnoid haemorrhage. Neurol Res 17:106–108. https://doi.org/10.1080/01616412.1995.11740296
55. Vikman P, Beg S, Khurana TS et al (2006) Gene expression and molecular changes in cerebral arteries following subarachnoid hemorrhage in the rat. J Neurosurg 105:438–444. https://doi.org/10.3171/jns.2006.105.3.438
56. Cahill J, Calvert JW, Zhang JH (2006) Mechanisms of early brain injury after subarachnoid hemorrhage. J Cereb Blood Flow Metab 26:1341–1353. https://doi.org/10.1038/sj.jcbfm.9600283
57. Muroi C, Fujioka M, Mishima K et al (2014) Effect of ADAMTS-13 on cerebrovascular microthrombosis and neuronal injury after experimental subarachnoid hemorrhage. J Thromb Haemost 12:505–514. https://doi.org/10.1111/jth.12511
58. Senchenkova EY, Komoto S, Russell J et al (2013) Interleukin-6 mediates the platelet abnormalities and thrombogenesis associated with experimental colitis. Am J Pathol 183:173–181. https://doi.org/10.1016/j.ajpath.2013.03.014
59. Grignani G, Maiolo A (2000) Cytokines and hemostasis. Haematologica 85:967–972
60. Bernardo A, Ball C, Nolasco L et al (2004) Effects of inflammatory cytokines on the release and cleavage of the endothelial cell-derived ultralarge von Willebrand factor multimers under flow. Blood 104:100–106. https://doi.org/10.1182/blood-2004-01-0107
61. Andereggen L, Neuschmelting V, Von Gunten M et al (2014) The role of microclot formation in an acute subarachnoid hemorrhage model in the rabbit. Biomed Res Int 2014:161702. https://doi.org/10.1155/2014/161702
62. Vergouwen MD, Bakhtiari K, Van Geloven N et al (2009) Reduced ADAMTS13 activity in delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J Cereb Blood Flow Metab 29:1734–1741. https://doi.org/10.1038/jcbfm.2009.88
63. Pisapia JM, Xu X, Kelly J et al (2012) Microthrombosis after experimental subarachnoid hemorrhage: time course and effect of red blood cell-bound thrombin-activated pro-urokinase and clazosentan. Exp Neurol 233:357–363. https://doi.org/10.1016/j.expneurol.2011.10.029
64. Biggioggero M, Crotti C, Becciolini A et al (2019) Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. Drug Des Devel Ther 13:57–70. https://doi.org/10.2147/dddt.S150580
65. Bijlsma JWJ, Welsing PMJ, Woodworth TG et al (2016) Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet 388:343–355. https://doi.org/10.1016/s0140-6736(16)30363-4
66. Bongartz T (2008) Tocilizumab for rheumatoid and juvenile idiopathic arthritis. Lancet 371:961–963. https://doi.org/10.1016/S0140-6736(08)60428-6
67. Hill JA, Menon MP, Dhanireddy S et al (2021) Tocilizumab in hospitalized patients with COVID-19: clinical outcomes, inflammatory marker kinetics, and safety. J Med Virol 93:2270–2280. https://doi.org/10.1002/jmv.26674
68. Wise J (2021) Covid-19: Arthritis drug tocilizumab reduces deaths in hospitalised patients, study shows. BMJ (Clinical research ed) 372:n433. https://doi.org/10.1136/bmj.n433
69. Zhao M, Lu J, Tang Y et al (2021) Tocilizumab for treating COVID-19: a systemic review and meta-analysis of retrospective studies. Eur J Clin Pharmacol 77:311–319. https://doi.org/10.1007/s00228-020-03017-5