ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of Gastroenterology®

Indexed and Abstracted in:
Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Digital Object Identifier. ISI, Thomson Reuters, 2009 Impact Factor: 2.092 (33/65 Gastroenterology and Hepatology).

Volume 16 Number 47
December 21, 2010
World J Gastroenterol
2010 December 21; 16(47): 5907-6034

Online Submissions
www.wjgnet.com/1007-9327office
www.wjgnet.com
Printed on Acid-free Paper
世界胃肠病学杂志

A Weekly Journal of Gastroenterology and Hepatology

World Journal of Gastroenterology

A peer-reviewed, online, open-access journal of gastroenterology and hepatology

Editorial Board

2010-2013

The *World Journal of Gastroenterology* Editorial Board consists of 1144 members, representing a team of worldwide experts in gastroenterology and hepatology. They are from 60 countries, including Albania (1), Argentina (8), Australia (29), Austria (14), Belgium (12), Brazil (10), Brunei Darussalam (1), Bulgaria (2), Canada (20), Chile (3), China (69), Colombia (1), Croatia (2), Cuba (1), Czech (4), Denmark (8), Ecuador (1), Egypt (2), Estonia (2), Finland (8), France (24), Germany (75), Greece (14), Hungary (10), India (26), Iran (6), Ireland (7), Israel (12), Italy (101), Japan (112), Jordan (1), Kuwait (1), Lebanon (3), Lithuania (2), Malaysia (1), Mexico (10), Moldova (1), Netherlands (29), New Zealand (2), Norway (11), Pakistan (2), Poland (11), Portugal (4), Romania (3), Russia (1), Saudi Arabia (3), Serbia (3), Singapore (10), South Africa (2), South Korea (32), Spain (38), Sweden (18), Switzerland (11), Thailand (1), Trinidad and Tobago (1), Turkey (24), United Arab Emirates (2), United Kingdom (82), United States (249), and Uruguay (1).

Robert JL Fraser, *Daw Park*
Jacob George, *Westmead*
Mark D Gorrell, *Sydney*
Alexander G Heriot, *Melbourne*
Michael Horowitz, *Adelaide*
John E Kellow, *Sydney*
William Kemp, *Melbourne*
Finlay A Macrae, *Victoria*
Daniel Markovich, *Brisbane*
Vance Matthews, *Melbourne*
Phillip S Oates, *Perth*
Shan Rajendra, *Tasmania*
Rajvinder Singh, *Elizabeth Vale*
Ross C Smith, *Sydney*
Kevin J Spring, *Brisbane*
Nathan Subramaniam, *Brisbane*
Phil Sutton, *Melbourne*
Cuong D Tran, *North Adelaide*
Debbie Trinder, *Fremantle*
David Ian Watson, *Bedford Park*

Austria

Herwig R Cerwenka, *Graz*
Ashraf Dahaba, *Graz*
Peter Ferenci, *Vienna*
Valentin Fuhrmann, *Vienna*
Alfred Gangl, *Vienna*
Alexander M Hirschl, *Wien*
Kurt Lenz, *Linz*
Dietmar Öfner, *Salzburg*
Markus Peck-Radosavljevic, *Vienna*
Markus Raderer, *Vienna*
Stefan Riss, *Vienna*
Georg Roth, *Vienna*
Michael Trauner, *Graz*
Thomas Wild, *Kapellerfeld*

Belgium

Rudi Beyaert, *Gent*
Benedicte Y De Winter, *Antwerp*
Inge I Depoortere, *Leuven*
Olivier Detry, *Liège*
Philip Meuleman, *Ghent*
Marc Peeters, *De Pintelaan*
Freddy Penninckx, *Leuven*
Jean-Yves L Reginster, *Liège*
Mark De Ridder, *Brussels*
Etienne M Sokal, *Brussels*
Kristin Verbeke, *Leuven*
Eddie Wisse, *Keerbergen*

Brazil

José LF Caboclo, *São José do Rio Preto*
Roberto J Carvalho-Filho, *São Paulo*
Jaime Natan Eisig, *São Paulo*
Andre Castro Lyra, *Salvador*
Marcelo Lima Ribeiro, *Braganca Paulista*
Joao Batista Teixeira Rocha, *Santa Maria*
Heitor Rosa, *Goiania*
Damiao C Moraes Santos, *Rio de Janeiro*
Ana Cristina Simões e Silva, *Belo Horizonte*
Eduardo Garcia Vilela, *Belo Horizonte*

Brunei Darussalam

Vui Heng Chong, *Bandar Seri Begawan*

Bulgaria

Zahariy Krastev, *Sofia*
Mihaela Petrova, *Sofia*

Canada

Alain Bitton, *Montreal*
Michael F Byrne, *Vancouver*
Kris Chadee, *Calgary*
Wangxue Chen, *Ottawa*
Ram Prakash Galwa, *Ottawa*
Philip H Gordon, *Montreal*
Waliul Khan, *Ontario*
Qiang Liu, *Saskatoon*
John K Marshall, *Ontario*
Andrew L Mason, *Alberta*
Kostas Pantopoulos, *Quebec*
Nathalie Perreault, *Sherbrooke*
Baljinder Singh Salh, *Vancouver*
Eldon Shaffer, *Calgary*
Martin Storr, *Calgary*
Pingchang Yang, *Hamilton*
Eric M Yoshida, *Vancouver*
Claudia Zwingmann, *Montreal*

Chile

Marcelo A Beltran, *La Serena*
Xabier De Aretxabala, *Santiago*
Silvana Zanlungo, *Santiago*

China

Hui-Jie Bian, *Xi'an*
San-Jun Cai, *Shanghai*
Guang-Wen Cao, *Shanghai*
Xiao-Ping Chen, *Wuhan*
Chi-Hin Cho, *Hong Kong*
Zong-Jie Cui, *Beijing*
Jing-Yuan Fang, *Shanghai*
De-Liang Fu, *Shanghai*
Ze-Guang Han, *Shanghai*
Chun-Yi Hao, *Beijing*
Ming-Liang He, *Hong Kong*
Ching-Lung Lai, *Hong Kong*
Simon Law, *Hong Kong*
Yuk-Tong Lee, *Hong Kong*
En-Min Li, *Shantou*
Fei Li, *Beijing*
Yu-Yuan Li, *Guangzhou*
Zhao-Shen Li, *Shanghai*
Xing-Hua Lu, *Beijing*
Yi-Min Mao, *Shanghai*
Qin Su, *Beijing*
Paul Kwong-Hang Tam, *Hong Kong*
Yuk Him Tam, *Hong Kong*
Ren-Xiang Tan, *Nanjing*
Wei-Dong Tong, *Chongqing*
Eric WC Tse, *Hong Kong*
Fu-Sheng Wang, *Beijing*
Xiang-Dong Wang, *Shanghai*
Nathalie Wong, *Hong Kong*
Justin CY Wu, *Hong Kong*
Wen-Rong Xu, *Zhenjiang*
An-Gang Yang, *Xi'an*
Wei-Cheng You, *Beijing*
Chun-Qing Zhang, *Jinan*
Jian-Zhong Zhang, *Beijing*
Xiao-Peng Zhang, *Beijing*
Xuan Zhang, *Beijing*

Colombia

Germán Campuzano-Maya, *Medellín*

Croatia

Tamara Cacev, *Zagreb*
Marko Duvnjak, *Zagreb*

Cuba

Damian C Rodriguez, *Havana*

Czech

Jan Bures, *Hradec Kralove*
Milan Jirsa, *Praha*
Marcela Kopacova, *Hradec Kralove*
Pavel Trunečka, *Prague*

Denmark

Leif Percival Andersen, *Copenhagen*
Asbjørn M Drewes, *Aalborg*
Morten Frisch, *Copenhagen*
Jan Mollenhauer, *Odense*
Morten Hylander Møller, *Holte*
Søren Rafaelsen, *Vejle*
Jorgen Rask-Madsen, *Skodsborg*
Peer Wille-Jørgensen, *Copenhagen*

Ecuador

Fernando E Sempértegui, *Quito*

Egypt

Zeinab Nabil Ahmed, *Cairo*
Hussein M Atta, *El-Minia*

Estonia

Riina Salupere, *Tartu*
Tamara Vorobjova, *Tartu*

Finland

Saila Kauhanen, *Turku*

Thomas Kietzmann, *Oulu*
Kaija-Leena Kolho, *Helsinki*
Jukka-Pekka Mecklin, *Jyvaskyla*
Minna Nyström, *Helsinki*
Pauli Antero Puolakkainen, *Turku*
Juhani Sand, *Tampere*
Lea Veijola, *Helsinki*

France

Claire Bonithon-Kopp, *Dijon*
Lionel Bueno, *Toulouse*
Sabine Colnot, *Paris*
Catherine Daniel, *Lille Cedex*
Alexis Desmoulière, *Limoges*
Thabut Dominique, *Paris*
Francoise L Fabiani, *Angers*
Jean-Luc Faucheron, *Grenoble*
Jean Paul Galmiche, *Nantes cedex*
Boris Guiu, *Dijon*
Paul Hofman, *Nice*
Laurent Huwart, *Paris*
Juan Iovanna, *Marseille*
Abdel-Majid Khatib, *Paris*
Philippe Lehours, *Bordeaux*
Flavio Maina, *Marseille*
Patrick Marcellin, *Paris*
Rene Gerolami Santandera, *Marseille*
Annie Schmid-Alliana, *Nice cedex*
Alain L Servin, *Châtenay-Malabry*
Stephane Supiot, *Nantes*
Baumert F Thomas, *Strasbourg*
Jean-Jacques Tuech, *Rouen*
Frank Zerbib, *Bordeaux Cedex*

Germany

Erwin Biecker, *Siegburg*
Hubert Blum, *Freiburg*
Thomas Bock, *Tuebingen*
Dean Bogoevski, *Hamburg*
Elfriede Bollschweiler, *Köln*
Jürgen Borlak, *Hannover*
Christa Buechler, *Regensburg*
Jürgen Büning, *Lübeck*
Elke Cario, *Essen*
Bruno Christ, *Halle/Saale*
Christoph F Dietrich, *Bad Mergentheim*
Ulrich R Fölsch, *Kiel*
Nikolaus Gassler, *Aachen*
Markus Gerhard, *Munich*
Dieter Glebe, *Giessen*
Ralph Graeser, *Freiburg*
Axel M Gressner, *Aachen*
Nils Habbe, *Marburg*
Thilo Hackert, *Heidelberg*
Wolfgang Hagmann, *Heidelberg*
Dirk Haller, *Freising*
Philip D Hard, *Giessen*
Claus Hellerbrand, *Regensburg*
Klaus R Herrlinger, *Stuttgart*
Eberhard Hildt, *Berlin*
Andrea Hille, *Goettingen*
Joerg C Hoffmann, *Berlin*
Philipe N Khalil, *Munich*
Andrej Khandoga, *Munich*
Jorg Kleeff, *Munich*
Ingmar Königsrainer, *Tübingen*
Peter Konturek, *Erlangen*
Stefan Kubicka, *Hannover*
Joachim Labenz, *Siegen*
Michael Linnebacher, *Rostock*
Jutta Elisabeth Lüttges, *Riegelsberg*
Peter Malfertheiner, *Magdeburg*
Oliver Mann, *Hamburg*
Peter N Meier, *Hannover*
Sabine Mihm, *Göttingen*
Klaus Mönkemüller, *Bottrop*
Jonas Mudter, *Erlangen*
Sebastian Mueller, *Heidelberg*
Robert Obermaier, *Freiburg*
Matthias Ocker, *Erlangen*
Stephan Johannes Ott, *Kiel*
Gustav Paumgartner, *Munich*
Christoph Reichel, *Bad Brückenau*
Markus Reiser, *Bochum*
Steffen Rickes, *Magdeburg*
Elke Roeb, *Giessen*
Christian Rust, *Munich*
Hans Scherubl, *Berlin*
Martin K Schilling, *Homburg*
Joerg F Schlaak, *Essen*
Rene Schmidt, *Freiburg*
Andreas G Schreyer, *Regensburg*
Karsten Schulmann, *Bochum*
Henning Schulze-Bergkamen, *Mainz*
Manfred V Singer, *Mannheim*
Jens Standop, *Bonn*
Jurgen M Stein, *Frankfurt*
Ulrike S Stein, *Berlin*
Wolfgang R Stremmel, *Heidelberg*
Harald F Teutsch, *Ulm*
Hans L Tillmann, *Leipzig*
Christian Trautwein, *Aachen*
Joerg Trojan, *Frankfurt*
Arndt Vogel, *Hannover*
Siegfried Wagner, *Deggendorf*
Frank Ulrich Weiss, *Greifswald*
Fritz von Weizsäcker, *Berlin*
Thomas Wex, *Magdeburg*
Stefan Wirth, *Wuppertal*
Marty Zdichavsky, *Tübingen*

Greece

Helen Christopoulou-Aletra, *Thessaloniki*
T Choli-Papadopoulou, *Thessaloniki*
Tsianos Epameinondas, *Ioannina*
Ioannis Kanellos, *Thessaloniki*
Elias A Kouroumalis, *Heraklion*
Ioannis E Koutroubakis, *Heraklion*
Michael Koutsilieris, *Athens*
Andreas Larentzakis, *Athens*
Emanuel K Manesis, *Athens*
Spilios Manolakopoulos, *Athens*
Konstantinos Mimidis, *Alexandroupolis*
George Papatheodoridis, *Athens*
Spiros Sgouros, *Athens*
Evangelos Tsiambas, *Ag Paraskevi Attiki*

Hungary

György M Buzás, *Budapest*
László Czakó, *Szeged*
Gyula Farkas, *Szeged*
Peter Hegyi, *Szeged*
Peter L Lakatos, *Budapest*
Yvette Mándi, *Szeged*
Zoltan Rakonczay, *Szeged*
Ferenc Sipos, *Budapest*
Zsuzsa Szondy, *Debrecen*
Gabor Veres, *Budapest*

India

Philip Abraham, *Mumbai*
Vineet Ahuja, *New Delhi*
Giriraj Ratan Chandak, *Hyderabad*
Devinder Kumar Dhawan, *Chandigarh*
Radha K Dhiman, *Chandigarh*
Pankaj Garg, *Panchkula*
Pramod Kumar Garg, *New Delhi*
Debidas Ghosh, *Midnpore*
Uday C Ghoshal, *Lucknow*
Bhupendra Kumar Jain, *Delhi*
Ashok Kumar, *Lucknow*
Bikash Medhi, *Chandigarh*
Sri P Misra, *Allahabad*
Gopal Nath, *Varanasi*
Samiran Nundy, *New Delhi*
Jagannath Palepu, *Mumbai*
Vandana Panda, *Mumbai*
Benjamin Perakath, *Tamil Nadu*
Ramesh Roop Rai, *Jaipur*
Nageshwar D Reddy, *Hyderabad*
Barjesh Chander Sharma, *New Delhi*
Virendra Singh, *Chandigarh*
Rupjyoti Talukdar, *Guwahati*
Rakesh Kumar Tandon, *New Delhi*
Jai Dev Wig, *Chandigarh*

Iran

Mohammad Abdollahi, *Tehran*
Peyman Adibi, *Isfahan*
Seyed-Moayed Alavian, *Tehran*
Seyed Mohsen Dehghani, *Shiraz*
Reza Malekzadeh, *Tehran*
Alireza Mani, *Tehran*

Ireland

Billy Bourke, *Dublin*
Ted Dinan, *Cork*
Catherine Greene, *Dublin*
Ross McManus, *Dublin*
Anthony P Moran, *Galway*
Marion Rowland, *Dublin*

Israel

Simon Bar-Meir, *Hashomer*
Alexander Becker, *Afula*
Abraham R Eliakim, *Haifa*
Sigal Fishman, *Tel Aviv*
Boris Kirshtein, *Beer Sheva*
Eli Magen, *Ashdod*
Menachem Moshkowitz, *Tel-Aviv*
Assy Nimer, *Safed*
Shmuel Odes, *Beer Sheva*
Mark Pines, *Bet Dagan*
Ron Shaoul, *Haifa*
Ami D Sperber, *Beer-Sheva*

Italy

Donato F Altomare, *Bari*
Piero Amodio, *Padova*
Angelo Andriulli, *San Giovanni Rotondo*
Paolo Angeli, *Padova*
Bruno Annibale, *Rome*
Paolo Aurello, *Rome*
Salvatore Auricchio, *Naples*
Antonio Basoli, *Rome*
Claudio Bassi, *Verona*
Gabrio Bassotti, *Perugia*
Mauro Bernardi, *Bologna*
Alberto Biondi, *Rome*
Luigi Bonavina, *Milano*
Guglielmo Borgia, *Naples*
Roberto Berni Canani, *Naples*
Maria Gabriella Caruso, *Bari*
Fausto Catena, *Bologna*
Giuseppe Chiarioni, *Valeggio*
Michele Cicala, *Rome*
Dario Conte, *Milano*
Francesco Costa, *Pisa*
Antonio Craxì, *Palermo*
Salvatore Cucchiara, *Rome*
Giuseppe Currò, *Messina*
Mario M D'Elios, *Florence*
Mirko D'Onofrio, *Verona*
Silvio Danese, *Milano*
Roberto de Franchis, *Milano*
Paola De Nardi, *Milan*
Giovanni D De Palma, *Naples*
Giuliana Decorti, *Trieste*
Gianlorenzo Dionigi, *Varese*
Massimo Falconi, *Verona*
Silvia Fargion, *Milan*
Giammarco Fava, *Ancona*
Francesco Feo, *Sassari*
Alessandra Ferlini, *Ferrara*
Alessandro Ferrero, *Torino*
Mirella Fraquelli, *Milan*
Luca Frulloni, *Verona*
Giovanni B Gaeta, *Napoli*
Antonio Gasbarrini, *Rome*
Edoardo G Giannini, *Genoa*
Alessandro Granito, *Bologna*
Fabio Grizzi, *Milan*
Salvatore Gruttadauria, *Palermo*
Pietro Invernizzi, *Milan*
Achille Iolascon, *Naples*
Angelo A Izzo, *Naples*
Ezio Laconi, *Cagliari*
Giovanni Latella, *L'Aquila*
Massimo Levrero, *Rome*
Francesco Luzza, *Catanzaro*
Lucia Malaguarnera, *Catania*
Francesco Manguso, *Napoli*
Pier Mannuccio Mannucci, *Milan*
Giancarlo Mansueto, *Verona*
Giulio Marchesini, *Bologna*
Mara Massimi, *Coppito*
Giovanni Milito, *Rome*
Giuseppe Montalto, *Palermo*
Giovanni Monteleone, *Rome*
Luca Morelli, *Trento*
Giovanni Musso, *Torino*
Mario Nano, *Torino*
Gerardo Nardone, *Napoli*
Riccardo Nascimbeni, *Brescia*
Valerio Nobili, *Rome*
Fabio Pace, *Milan*
Nadia Peparini, *Rome*
Marcello Persico, *Naples*
Mario Pescatori, *Rome*
Raffaele Pezzilli, *Bologna*
Alberto Piperno, *Monza*
Anna C Piscaglia, *Rome*
Piero Portincasa, *Bari*
Michele Reni, *Milan*
Vittorio Ricci, *Pavia*
Oliviero Riggio, *Rome*
Mario Rizzetto, *Torino*
Ballarin Roberto, *Modena*
Gerardo Rosati, *Potenza*
Franco Roviello, *Siena*
Cesare Ruffolo, *Treviso*
Massimo Rugge, *Padova*
Marco Scarpa, *Padova*
C armelo Scarpignato, *Parma*
Giuseppe Sica, *Rome*
Marco Silano, *Rome*
Pierpaolo Sileri, *Rome*
Vincenzo Stanghellini, *Bologna*
Fiorucci Stefano, *Perugia*
Giovanni Tarantino, *Naples*
Alberto Tommasini, *Trieste*
Guido Torzilli, *Rozzano Milan*
Cesare Tosetti, *Porretta Terme*
Antonello Trecca, *Rome*
Vincenzo Villanacci, *Brescia*
Lucia Ricci Vitiani, *Rome*
Marco Vivarelli, *Bologna*

Japan

Kyoichi Adachi, *Izumo*
Yasushi Adachi, *Sapporo*
Takafumi Ando, *Nagoya*
Akira Andoh, *Otsu*
Masahiro Arai, *Tokyo*
Hitoshi Asakura, *Tokyo*
Kazuo Chijiiwa, *Miyazaki*
Yuichiro Eguchi, *Saga*
Itaru Endo, *Yokohama*
Munechika Enjoji, *Fukuoka*
Yasuhiro Fujino, *Akashi*
Mitsuhiro Fujishiro, *Tokyo*
Kouhei Fukushima, *Sendai*
Masanori Hatakeyama, *Tokyo*
Keiji Hirata, *Kitakyushu*
Toru Hiyama, *Higashihiroshima*
Masahiro Iizuka, *Akita*
Susumu Ikehara, *Osaka*
Kenichi Ikejima, *Bunkyo-ku*
Yutaka Inagaki, *Kanagawa*
Hiromi Ishibashi, *Nagasaki*
Shunji Ishihara, *Izumo*
Toru Ishikawa, *Niigata*
Toshiyuki Ishiwata, *Tokyo*
Hajime Isomoto, *Nagasaki*
Yoshiaki Iwasaki, *Okayama*
Satoru Kakizaki, *Gunma*
Terumi Kamisawa, *Tokyo*
Mototsugu Kato, *Sapporo*
Naoya Kato, *Tokyo*
Takumi Kawaguchi, *Kurume*
Yohei Kida, *Kainan*
Shogo Kikuchi, *Aichi*
Tsuneo Kitamura, *Chiba*
Takashi Kobayashi, *Tokyo*
Yasuhiro Koga, *Isehara*
Takashi Kojima, *Sapporo*
Norihiro Kokudo, *Tokyo*
Masatoshi Kudo, *Osaka*
Shin Maeda, *Tokyo*
Satoshi Mamori, *Hyogo*
Atsushi Masamune, *Sendai*
Yasushi Matsuzaki, *Tsukuba*
Kenji Miki, *Tokyo*
Toshihiro Mitaka, *Sapporo*
Hiroto Miwa, *Hyogo*
Kotaro Miyake, *Tokushima*
Manabu Morimoto, *Yokohama*
Yoshiharu Motoo, *Kanazawa*
Yoshiaki Murakami, *Hiroshima*
Yoshiki Murakami, *Kyoto*
Kunihiko Murase, *Tusima*
Akihito Nagahara, *Tokyo*
Yuji Naito, *Kyoto*
Atsushi Nakajima, *Yokohama*
Hisato Nakajima, *Tokyo*
Hiroki Nakamura, *Yamaguchi*
Shotaro Nakamura, *Fukuoka*
Akimasa Nakao, *Nagogya*
Shuhei Nishiguchi, *Hyogo*
Mikio Nishioka, *Niihama*
Keiji Ogura, *Tokyo*
Susumu Ohmada, *Maebashi*
Hirohide Ohnishi, *Akita*
Kenji Okajima, *Nagoya*
Kazuichi Okazaki, *Osaka*
Morikazu Onji, *Ehime*
Satoshi Osawa, *Hamamatsu*
Hidetsugu Saito, *Tokyo*
Yutaka Saito, *Tokyo*
Naoaki Sakata, *Sendai*
Yasushi Sano, *Chiba*
Tokihiko Sawada, *Tochigi*
Tomohiko Shimatan, *Hiroshima*
Yukihiro Shimizu, *Kyoto*
Shinji Shimoda, *Fukuoka*
Yoshio Shirai, *Niigata*
Masayuki Sho, *Nara*
Shoichiro Sumi, *Kyoto*
Hidekazu Suzuki, *Tokyo*
Masahiro Tajika, *Nagoya*
Yoshihisa Takahashi, *Tokyo*
Toshinari Takamura, *Kanazawa*
Hiroaki Takeuchi, *Kochi*
Yoshitaka Takuma, *Okayama*
Akihiro Tamori, *Osaka*
Atsushi Tanaka, *Tokyo*
Shinji Tanaka, *Hiroshima*
Satoshi Tanno, *Hokkaido*
Shinji Togo, *Yokohama*
Hitoshi Tsuda, *Tokyo*
Hiroyuki Uehara, *Osaka*
Masahito Uemura, *Kashihara*
Yoshiyuki Ueno, *Sendai*
Mitsuyoshi Urashima, *Tokyo*
Takuya Watanabe, *Niigata*
Satoshi Yamagiwa, *Niigata*
Taketo Yamaguchi, *Chiba*
Mitsunori Yamakawa, *Yamagata*
Takayuki Yamamoto, *Yokkaichi*
Yutaka Yata, *Maebashi*
Hiroshi Yoshida, *Tokyo*
Norimasa Yoshida, *Kyoto*
Yuichi Yoshida, *Osaka*
Kentaro Yoshika, *Toyoake*
Hitoshi Yoshiji, *Nara*
Katsutoshi Yoshizato, *Higashihiroshima*
Tomoharu Yoshizumi, *Fukuoka*

Jordan

Ismail Matalka, *Irbid*

Kuwait

Islam Khan, *Safat*

Lebanon

Bassam N Abboud, *Beirut*
Ala I Sharara, *Beirut*
Rita Slim, *Beirut*

Lithuania

Giedrius Barauskas, *Kaunas*
Limas Kupcinskas, *Kaunas*

Malaysia

Andrew Seng Boon Chua, *Ipoh*

Mexico

Richard A Awad, *Mexico*
Aldo Torre Delgadillo, *Mexico*
Diego Garcia-Compean, *Monterrey*
Paulino M Hernández Magro, *Celaya*
Miguel Angel Mercado, *Distrito Federal*
Arturo Panduro, *Jalisco*
Omar Vergara-Fernandez, *Tlalpan*
Saúl Villa-Trevio, *Mexico*

Moldova

Igor Mishin, *Kishinev*

Netherlands

Ulrich Beuers, *Amsterdam*
Lee Bouwman, *Leiden*
Albert J Bredenoord, *Nieuwegein*
Lodewijk AA Brosens, *Utrecht*
J Bart A Crusius, *Amsterdam*
Wouter de Herder, *Rotterdam*
Pieter JF de Jonge, *Rotterdam*
Robert J de Knegt, *Rotterdam*
Wendy W Johanna de Leng, *Utrecht*
Annemarie de Vries, *Rotterdam*
James CH Hardwick, *Leiden*
Frank Hoentjen, *Haarlem*
Misha Luyer, *Sittard*
Jeroen Maljaars, *Maastricht*
Gerrit A Meijer, *Amsterdam*
Servaas Morré, *Amsterdam*
Chris JJ Mulder, *Amsterdam*
John Plukker, *Groningen*
Albert Frederik Pull ter Gunne, *Tilburg*
Paul E Sijens, *Groningen*
BW Marcel Spanier, *Arnhem*
Shiri Sverdlov, *Maastricht*
Maarten Tushuizen, *Amsterdam*
Jantine van Baal, *Heidelberglaan*
Astrid van der Velde, *The Hague*
Karel van Erpecum, *Utrecht*
Loes van Keimpema, *Nijmegen*
Robert Christiaan Verdonk, *Groningen*
Erwin G Zoetendal, *Wageningen*

New Zealand

Andrew S Day, *Christchurch*

Norway

Olav Dalgard, *Oslo*
Trond Peder Flaten, *Trondheim*
Reidar Fossmark, *Trondheim*
Rasmus Goll, *Tromso*
Ole Høie, *Arendal*
Asle W Medhus, *Oslo*
Espen Melum, *Oslo*
Trine Olsen, *Tromso*
Eyvind J Paulssen, *Tromso*
Jon Arne Søreide, *Stavanger*
Kjetil Soreide, *Stavanger*

Pakistan

Shahab Abid, *Karachi*
Syed MW Jafri, *Karachi*

Poland

Marek Bebenek, *Wroclaw*
Tomasz Brzozowski, *Cracow*
Halina Cichoż-Lach, *Lublin*
Andrzej Dabrowski, *Bialystok*
Hanna Gregorek, *Warsaw*
Marek Hartleb, *Katowice*
Beata Jolanta Jabłońska, *Katowice*
Stanislaw J Konturek, *Krakow*
Jan Kulig, *Krakow*
Dariusz M Lebensztejn, *Bialystok*
Julian Swierczynski, *Gdansk*

Portugal

Raquel Almeida, *Porto*
Ana Isabel Lopes, *Lisboa Codex*
Ricardo Marcos, *Porto*
Guida Portela-Gomes, *Estoril*

Romania

Dan L Dumitrascu, *Cluj*
Adrian Saftoiu, *Craiova*
Andrada Seicean, *Cluj-Napoca*

Russia

Vasiliy I Reshetnyak, *Moscow*

Saudi Arabia

Ibrahim A Al Mofleh, *Riyadh*
Abdul-Wahed Meshikhes, *Qatif*
Faisal Sanai, *Riyadh*

Serbia

Tamara M Alempijevic, *Belgrade*
Dusan M Jovanovic, *Sremska Kamenica*
Zoran Krivokapic, *Belgrade*

Singapore

Madhav Bhatia, *Singapore*
Kong Weng Eu, *Singapore*
Brian Kim Poh Goh, *Singapore*
Khek-Yu Ho, *Singapore*
Kok Sun Ho, *Singapore*
Fock Kwong Ming, *Singapore*
London Lucien Ooi, *Singapore*
Nagarajan Perumal, *Singapore*
Francis Seow-Choen, *Singapore*

South Africa

Rosemary Joyce Burnett, *Pretoria*
Michael Kew, *Cape Town*

South Korea

Sang Hoon Ahn, *Seoul*
Sung-Gil Chi, *Seoul*
Myung-Gyu Choi, *Seoul*
Hoon Jai Chun, *Seoul*
Yeun-Jun Chung, *Seoul*
Young-Hwa Chung, *Seoul*
Kim Donghee, *Seoul*
Ki-Baik Hahm, *Incheon*
Sun Pyo Hong, *Geonggi-do*
Seong Gyu Hwang, *Seongnam*
Hong Joo Kim, *Seoul*
Jae J Kim, *Seoul*
Jin-Hong Kim, *Suwon*
Nayoung Kim, *Seongnam-si*
Sang Geon Kim, *Seoul*
Seon Hahn Kim, *Seoul*
Sung Kim, *Seoul*
Won Ho Kim, *Seoul*
Jeong Min Lee, *Seoul*
Kyu Taek Lee, *Seoul*
Sang Kil Lee, *Seoul*
Sang Yeoup Lee, *Gyeongsangnam-do*
Yong Chan Lee, *Seoul*
Eun-Yi Moon, *Seoul*
Hyoung-Chul Oh, *Seoul*
Seung Woon Paik, *Seoul*
Joong-Won Park, *Goyang*
Ji Kon Ryu, *Seoul*
Si Young Song, *Seoul*
Marie Yeo, *Suwon*
Byung Chul Yoo, *Seoul*
Dae-Yeul Yu, *Daejeon*

Spain

Maria-Angeles Aller, *Madrid*
Raul J Andrade, *Málaga*
Luis Aparisi, *Valencia*
Gloria González Aseguinolaza, *Navarra*
Matias A Avila, *Pamplona*

Fernando Azpiroz, *Barcelona*
Ramon Bataller, *Barcelona*
Belén Beltrán, *Valencia*
Adolfo Benages, *Valencia*
Josep M Bordas, *Barcelona*
Lisardo Boscá, *Madrid*
Luis Bujanda, *San Sebastián*
Juli Busquets, *Barcelona*
Matilde Bustos, *Pamplona*
José Julián calvo Andrés, *Salamanca*
Andres Cardenas, *Barcelona*
Antoni Castells, *Barcelona*
Fernando J Corrales, *Pamplona*
J E Domínguez-Muñoz, *Santiago de Compostela*
Juan Carlos Laguna Egea, *Barcelona*
Isabel Fabregat, *Barcelona*
Antoni Farré, *Barcelona*
Vicente Felipo, *Valencia*
Laureano Fernández-Cruz, *Barcelona*
Luis Grande, *Barcelona*
Angel Lanas, *Zaragoza*
Juan-Ramón Larrubia, *Guadalajara*
María IT López, *Jaén*
Juan Macías, *Seville*
Javier Martin, *Granada*
José Manuel Martin-Villa, *Madrid*
Julio Mayol, *Madrid*
Mireia Miquel, *Sabadell*
Albert Parés, *Barcelona*
Jesús M Prieto, *Pamplona*
Pedro L Majano Rodriguez, *Madrid*
Joan Roselló-Catafau, *Barcelona*
Eva Vaquero, *Barcelona*

Sweden

Lars Erik Agréus, *Stockholm*
Mats Andersson, *Stockholm*
Roland Andersson, *Lund*
Mauro D'Amato, *Huddinge*
Evangelos Kalaitzakis, *Gothenburg*
Greger Lindberg, *Stockholm*
Annika Lindblom, *Stockholm*
Sara Lindén, *Göteborg*
Hanns-Ulrich Marschall, *Stockholm*
Pär Erik Myrelid, *Linköping*
Åke Nilsson, *Lund*
Helena Nordenstedt, *Stockholm*
Kjell Öberg, *Uppsala*
Lars A Pahlman, *Uppsala*
Stefan G Pierzynowski, *Lund*
Sara Regnér, *Malmö*
Bobby Tingstedt, *Lund*
Zongli Zheng, *Stockholm*

Switzerland

Pascal Bucher, *Geneva*
Michelangelo Foti, *Geneva*
Jean L Frossard, *Geneva*
Andreas Geier, *Zürich*
Pascal Gervaz, *Geneva*
Gerd A Kullak-Ublick, *Zürich*
Fabrizio Montecucco, *Geneva*
Paul M Schneider, *Zürich*
Felix Stickel, *Berne*
Bruno Stieger, *Zürich*
Inti Zlobec, *Basel*

Trinidad and Tobago

Shivananda Nayak, *Mount Hope*

Turkey

Sinan Akay, *Tekirdag*
Metin Basaranoglu, *Istanbul*
Yusuf Bayraktar, *Ankara*
A Mithat Bozdayi, *Ankara*
Hayrullah Derici, *Balıkesir*
Eren Ersoy, *Ankara*
Mukaddes Esrefoglu, *Malatya*
Can Goen, *Kutahya*
Selin Kapan, *Istanbul*
Aydin Karabacakoglu, *Konya*
Cuneyt Kayaalp, *Malatya*
Kemal Kismet, *Ankara*
Seyfettin Köklü, *Ankara*
Mehmet Refik Mas, *Etlik-Ankara*
Osman C Ozdogan, *Istanbul*
Bülent Salman, *Ankara*
Orhan Sezgin, *Mersin*
Ilker Tasci, *Ankara*
Müge Tecder-Ünal, *Ankara*
Ahmet Tekin, *Mersin*
Mesut Tez, *Ankara*
Ekmel Tezel, *Ankara*
Özlem Yilmaz, *Izmir*

United Arab Emirates

Fikri M Abu-Zidan, *Al-Ain*
Sherif M Karam, *Al-Ain*

United Kingdom

Simon Afford, *Birmingham*
Navneet K Ahluwalia, *Stockport*
Mohamed H Ahmed, *Southampton*
Basil Ammori, *Salford*
Lesley A Anderson, *Belfast*
Chin Wee Ang, *Liverpool*
Yeng S Ang, *Wigan*
Anthony TR Axon, *Leeds*
Kathleen B Bamford, *London*
Jim D Bell, *London*
John Beynon, *Swansea*
Chris Briggs, *Sheffield*
Geoffrey Burnstock, *London*
Alastair D Burt, *Newcastle*
Jeff Butterworth, *Shrewsbury*
Jeremy FL Cobbold, *London*
Jean E Crabtree, *Leeds*
Tatjana Crnogorac-Jurcevic, *London*
William Dickey, *Londonderry*
Sunil Dolwani, *Cardiff*
Emad M El-Omar, *Aberdeen*
A M El-Tawil, *Birmingham*
Charles B Ferguson, *Belfast*
Andrew Fowell, *Southampton*
Piers Gatenby, *London*
Daniel R Gaya, *Edinburgh*
Anil George, *London*
Rob Glynne-Jones, *Northwood*
Jason CB Goh, *Birmingham*
Gianpiero Gravante, *Leicester*
Brian Green, *Belfast*
William Greenhalf, *Liverpool*
Indra N Guha, *Nottingham*
Stefan G Hübscher, *Birmingham*
Robin Hughes, *London*
Pali Hungin, *Stockton*
Nawfal Hussein, *Nottingham*
Clement W Imrie, *Glasgow*
Janusz AZ Jankowski, *Oxford*
Sharad Karandikar, *Birmingham*
Peter Karayiannis, *London*
Shahid A Khan, *London*
Patricia F Lalor, *Birmingham*
John S Leeds, *Sheffield*
Ian Lindsey, *Oxford*
Hong-Xiang Liu, *Cambridge*
Dileep N Lobo, *Nottingham*
Graham MacKay, *Glasgow*
Mark Edward McAlindon, *Sheffield*
Anne McCune, *Bristol*
Donald Campbell McMillan, *Glasgow*
Giorgina Mieli-Vergani, *London*
Jamie Murphy, *London*
Guy Fairbairn Nash, *Poole*
James Neuberger, *Birmingham*
Patrick O'Dwyer, *Glasgow*
Christos Paraskeva, *Bristol*
Richard Parker, *North Staffordshire*
Thamara Perera, *Birmingham*
Kondragunta Rajendra Prasad, *Leeds*
D Mark Pritchard, *Liverpool*
Alberto Quaglia, *London*
Akhilesh B Reddy, *Cambridge*
Kevin Robertson, *Glasgow*
Sanchoy Sarkar, *Liverpool*
John B Schofield, *Kent*
Marco Senzolo, *Padova*
Venkatesh Shanmugam, *Derby*
Paul Sharp, *London*
Chew Thean Soon, *Manchester*
Aravind Suppiah, *East Yorkshire*
Noriko Suzuki, *Middlesex*
Simon D Taylor-Robinson, *London*
Frank I Tovey, *London*
A McCulloch Veitch, *Wolverhampton*
Vamsi R Velchuru, *Lowestoft*
Sumita Verma, *Brighton*
Catherine Walter, *Cheltenham*
Julian RF Walters, *London*
Roger Williams, *London*

United States

Kareem M Abu-Elmagd, *Pittsburgh*
Sami R Achem, *Florida*
Golo Ahlenstiel, *Bethesda*
Bhupinder S Anand, *Houston*
M Ananthanarayanan, *New York*
Balamurugan N Appakalal, *Minneapolis*
Dimitrios V Avgerinos, *New York*
Shashi Bala, *Worcester*
Anthony J Bauer, *Pittsburgh*
Kevin E Behrns, *Gainesville*
Roberto Bergamaschi, *New York*
Henry J Binder, *New Haven*
Edmund J Bini, *New York*
Wojciech Blonski, *Philadelphia*
Mark Bloomston, *Columbus*
Edward L Bradley III, *Sarasota*
Carla W Brady, *Durham*

WJG World Journal of Gastroenterology

Contents

Weekly Volume 16 Number 47 December 21, 2010

World Journal of Gastroenterology
Volume 16 Number 47 December 21, 2010

Contents

NAME OF JOURNAL
World Journal of Gastroenterology

LAUNCH DATE
October 1, 1995

RESPONSIBLE INSTITUTION
Department of Science and Technology of Shanxi Province

SPONSOR
Taiyuan Research and Treatment Center for Digestive Diseases, 77 Shuangta Xijie, Taiyuan 030001, Shanxi Province, China

EDITING
Editorial Board of *World Journal of Gastroenterology*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0039
Fax: +86-10-8538-1893
E-mail: wjg@wjgnet.com
http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-3115-8812
Telephone: +852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

PRINT SUBSCRIPTION
RMB 245 Yuan for each issue, RMB 11760 Yuan for one year.

ONLINE SUBSCRIPTION
One-Year Price 864.00 USD

PUBLICATION DATE
December 21, 2010

CSSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1007-9327/g_info_20100315215714.htm. If you do not have web access please contact the editorial office.

ONLINE SUBMISSION
http://www.wjgnet.com/1007-9327office

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i47.6001

World J Gastroenterol 2010 December 21; 16(47): 6001-6009
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Immune phenotype in children with therapy-naïve remitted and relapsed Crohn's disease

Aron Cseh, Barna Vasarhelyi, Kriszta Molnar, Balazs Szalay, Peter Svec, Andras Treszl, Antal Dezsofi, Peter Laszlo Lakatos, Andras Arato, Tivadar Tulassay, Gabor Veres

Aron Cseh, Barna Vasarhelyi, Kriszta Molnar, Balazs Szalay, Peter Svec, Andras Treszl, Research Group for Pediatrics and Nephrology, Semmelweis University and Hungarian Academy of Sciences, H-1083, Budapest, Hungary
Barna Vasarhelyi, Department of Laboratory Medicine, Semmelweis University, H-1083, Budapest, Hungary
Antal Dezsofi, Andras Arato, Tivadar Tulassay, Gabor Veres, First Department of Pediatrics, Semmelweis University, H-1083, Budapest, Hungary
Peter Laszlo Lakatos, First Department of Medicine, Semmelweis University, H-1083, Budapest, Hungary
Author contributions: Veres G and Cseh A designed the research; Dezsofi A, Lakatos PL, Arato A and Veres G included the patients; Cseh A, Molnar K, Szalay B and Svec P performed the analyses; Treszl A analyzed the data; Cseh A, Vasarhelyi B and Veres G wrote the paper; Tulassay T critically reviewed the paper.
Supported by Grants TÁMOP-4.2.2-08/1/KMR-2008-0004, OTKA-76316, OTKA-K81117 and ETT-028-02
Correspondence to: Aron Cseh, MD, Research Group for Pediatrics and Nephrology, Semmelweis University and Hungarian Academy of Sciences, H-1083, Budapest, Hungary. cseharon@gmail.com
Telephone: +36-1-4591500 Fax: +36-1-3036077
Received: March 1, 2010 Revised: June 1, 2010
Accepted: June 8, 2010
Published online: December 21, 2010

Abstract

AIM: To characterize the prevalence of subpopulations of $CD4^+$ cells along with that of major inhibitor or stimulator cell types in therapy-naïve childhood Crohn's disease (CD) and to test whether abnormalities of immune phenotype are normalized with the improvement of clinical signs and symptoms of disease.

METHODS: We enrolled 26 pediatric patients with CD. 14 therapy-naïve CD children; of those, 10 children remitted on conventional therapy and formed the remission group. We also tested another group of 12 children who relapsed with conventional therapy and were given infliximab; and 15 healthy children who served as controls. The prevalence of Th1 and Th2, naïve and memory, activated and regulatory T cells, along with the members of innate immunity such as natural killer (NK), NK-T, myeloid and plasmocytoid dendritic cells (DCs), monocytes and Toll-like receptor (TLR)-2 and TLR-4 expression were determined in peripheral blood samples.

RESULTS: Children with therapy-naïve CD and those in relapse showed a decrease in Th1 cell prevalence. Simultaneously, an increased prevalence of memory and activated lymphocytes along with that of DCs and monocytes was observed. In addition, the ratio of myeloid /plasmocytoid DCs and the prevalence of TLR-2 or TLR-4 positive DCs and monocytes were also higher in therapy-naïve CD than in controls. The majority of alterations diminished in remitted CD irrespective of whether remission was obtained by conventional or biological therapy.

CONCLUSION: The finding that immune phenotype is normalized in remission suggests a link between immune phenotype and disease activity in childhood CD. Our observations support the involvement of members of the adaptive and innate immune systems in childhood CD.

Key words: Crohn's disease; Dendritic cell; Infliximab; Lymphocyte; Monocyte; Regulatory T cell; Relapse; Remission; Therapy-naïve; Toll-like receptor

Peer reviewers: Dr. Stefan Wirth, Professor, Children's Hospital, Heusnerstt. 40, Wuppertal 42349, Germany; Masahiro Iizuka, MD, PhD, Director, Akita Health Care Center, Akita Red Cross Hospital, 3-4-23, Nakadori, Akita 010-0001, Japan

Cseh A, Vasarhelyi B, Molnar K, Szalay B, Svec P, Treszl A, Dezsofi A, Lakatos PL, Arato A, Tulassay T, Veres G. Immune

phenotype in children with therapy-naïve remitted and relapsed Crohn's disease. *World J Gastroenterol* 2010; 16(47): 6001-6009 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i47/6001.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i47.6001

INTRODUCTION

Crohn's disease (CD) is a chronic gastrointestinal disease characterized by segmental inflammation of the intestinal mucosa associated with a dysregulated action of the mucosal immune system to the otherwise innocuous luminal antigens in a genetically susceptible host. About 10%-15% of patients with CD are diagnosed before 18 years of age[1]. Certain features are unique to pediatric CD in comparison to adult onset disease such as different disease location, altered response to immunosuppressive therapy and different genetic and immune phenotype[2,3]. Different characteristics may suggest differences in the pathomechanism of CD in children compared to that in adults. Theories regarding CD pathomechanism include malfunctioning of the immune system. Indeed, several studies carried out in adult CD indicate the involvement of either adaptive or innate immunity[4-7].

In adult CD, peripheral Treg prevalence is diminished in therapy-naïve patients and in the active state of disease or relapses and is increased with therapy or in remission[8-10], while intestinal Treg prevalence is increased in active CD[9-11]. Simultaneously, the prevalence of effector T cells[12-14] and activated T cells[15-17] is increased in the periphery in active CD. The shift of T lymphocytes toward Th1 commitment in peripheral blood and biopsy specimens is a widely observed phenomenon in CD[18].

In addition, the prevalence of antigen presenting cells (APCs) including dendritic cells (DCs) decrease in remission, and even more so in relapses at the periphery, but is increased in tissues, simultaneously with an increased expression of Toll-like receptor (TLR)-2 and 4 in therapy-naïve and treated CD adults[19-21]. Monocytes/macrophages, another group of APCs, are comparable at the periphery but increased in biopsies and showed upregulation of TLR-2 and TLR-4 in the active state and in remission of CD[22-25]. Other cell types of innate immunity such as natural killer (NK) and natural killer T (NKT) cells are less prevalent in active CD[17,26-28].

There have been a limited number of studies specifically performed to investigate alterations of the immune system in children with CD. In addition, the majority of available data are on treated CD children. While in untreated CD children some alterations in adaptive immunity have been reported, such as the skewness of the Th1/Th2 ratio to Th2 (this finding is in contrast with that observed in adult CD)[29-32], recent data suggest that the disturbance of innate immune functions is also a major factor contributing to CD in children. Indeed, in untreated children the central macrophage prevalence is increased[33], and TLR-2 and 4 receptor expression is also enhanced[34]. The role of innate immune system in the pathomechanism of CD may be inversely associated with age at disease onset[2].

The immune dysregulation in CD is affected by ongoing therapy. Aminosalicylates and steroids, as well as immunosuppressive drugs used as first-line therapy in CD have strong immunomodulatory effects[35]. In addition, biological therapy including the tumor necrosis factor α inhibitor infliximab (IFX)[36] also has substantial effects on immune cell functions [many of the data are from patients with rheumatoid arthritis (RA)] as it may increase the prevalence of peripheral and central Tregs[8,37], effector and activated[38,39] and Th1 committed T cells[39,40]. IFX also decreases the prevalence of NK cells[38], DCs[41,42] and monocytes[43,44], as well as TLR-2 and TLR-4 expression in peripheral cells[45]. The immunological impact of conventional or IFX therapy on peripheral immune phenotype is, however, known exclusively for adult CD patients and has not been explored fully in CD children.

In this prospective study we aimed to explore the major cell prevalence of the adaptive and innate immune systems in therapy-naïve CD children and its alteration with the improvement of CD obtained by conventional therapy or IFX treatment.

MATERIALS AND METHODS

We enrolled the following patient groups into our study: (1) 14 therapy-naïve CD children. No drug was prescribed for these patients at the time of CD diagnosis. The diagnosis of CD was established by means of "The Porto criteria"[46]; disease activity was determined according to the Pediatric Crohn's disease activity index (PCDAI)[47]; (2) During conventional treatment [steroid, azathioprine (AZT) and 5-aminosalicylate (5-ASA)], 10 children responded forming the remission group. Clinical remission was defined as a PCDAI < 10; (3) IFX therapy (5 mg/kg IFX at weeks 0, 2, and 6) was started in 12 CD children who failed to respond to conventional therapy forming the "relapsed group". Non-responsiveness was defined as moderately increased PCDAI (PCDAI > 30) in patients under conventional therapy; and (4) Fifteen age- and gender-matched children with functional abdominal pain served as controls. All patients and controls were diagnosed, treated and followed up in the Outpatient Clinic of the First Department of Pediatrics, Semmelweis University between September 2007 and August 2009. The Institutional Ethical Committee approved our study; written parental informed consent was obtained.

The patients' clinical characteristics are shown in Table 1. Small and large bowel was involved in 11 of 14 treatment naïve CD patients, according to the literature (L3 localization, Montreal criteria[48]). Therapy-naïve CD patients and CD patients with relapse had lower body mass index than controls. Lower body weight and body mass index is a common presenting sign in pediatric patients with CD[49]. Reduced food intake, postprandial abdominal cramps, systemic release of cytokines and malabsorptive diarrhea were listed as factors responsible for this phenomenon[50].

Table 1 Clinical data and patient characteristics

	Control	Therapy-naïve (before conventional therapy)	First remission (with conventional therapy)	Relapse (before IFX therapy)	IFX therapy (before 2nd infusion)	IFX therapy (before 3rd infusion)
Clinical data						
n (boys/girls)	15 (6/9)	14 (6/8)	10 (4/6)		12 (5/7)	
Age (yr)	12 (8-16)	10 (8.5-13)	11.5 (9.5-15.5)	14 (11-16)	14.5 (11.5-16)	14.5 (12-16)
Body mass index (kg/m^2)	19.5 (16.5-22.3)	13.9 (12.5-15.8)^{d}	18.6 (14.4-19.2)^{c}	17.4 (14.1-19.5)^{a}	18.8 (14.6-21.3)	19.25 (16.1-22.1)
Body weight (percentile)	58 (35-79)	13 (4-23)^{d}	24 (19-44)^{c}	21 (7-28)^{a}	23 (15-63)	35 (10-74)
Disease duration (mo)	-	10 (8.5-13)	10.5 (8.5-15.5)	11.5 (9.25-15)	12 (9.5-15)	12 (10-15)
Activity index (PCDAI)	-	45 (39-58)	0 (0-5)^{f}	45 (25-48)^{j}	20 (7-28)^{g}	13 (2-22)^{l}
Localization (*n*, montreal criteria)	-	L1 (1), L2 (2), L3 (11)	L1 (0), L2 (2), L3 (8)		L1 (1), L2 (2), L3 (9)	
Laboratory data						
White blood cell count (g/L)	7.9 (5.7-10.1)	12.4 (9.4-14.2)^{b}	11.7 (8.4-14.4)	10 (8.2-11.2)	7.9 (5.5-10.6)	6.7 (4.5-10.4)^{e}
Platelet (g/L)	346 (288-375)	657 (451-746)^{b}	442 (308-624)	479 (396-750)^{b}	392 (293-523)	383 (308-483)^{e}
Serum iron (μmol/L)	16 (14-21)	4 (2-12)^{a}	8 (4-10)^{a}	4 (2-7)^{d}	5 (4-7)^{d}	8 (6-8)^{b,e}
Serum albumin (g/L)	45 (44-49)	37 (34-39)^{d}	42 (42-45)^{c}	40 (36-41)^{d}	41 (38-45)^{b}	42 (38-45)^{b}
C-reactive protein (mg/L)	0 (0-1)	21 (5-65)^{d}	7 (2-11)^{b,c}	27 (9-55)^{h,d}	9 (3-11)^{d}	5 (1-14)^{d,e}

$^{a}P < 0.05$, $^{b}P < 0.01$; $^{d}P < 0.01$ *vs* control; $^{c}P < 0.05$, $^{f}P < 0.01$ *vs* therapy-naïve; $^{h}P < 0.01$, $^{j}P < 0.01$ *vs* first remission; $^{e}P < 0.05$, $^{g}P < 0.05$, $^{l}P < 0.001$ *vs* relapse. IFX: Infliximab; PCDAI: Pediatric Crohn's disease activity index; L1: Small bowel; L2: Large bowel; L3: Small bowel and large bowel localization according to Montreal criteria[48].

Together with other routine blood sampling 6 mL of lithium-heparin anticoagulated blood was taken from therapy-naïve patients at the time of diagnosis, at the time of first remission in the remission group and at the initiation of IFX therapy, and then 2 and 6 wk later in the relapsed groups. From peripheral blood mononuclear cells (PBMCs), the identification of markers (6B11, CCR4, CD3, CD4, CD8, CD11c, CD14, CD25, CD45RA, CD45RO, CD123; CD161, CXCR3, HLA-DR and Lin-1 BD Biosciences Pharmingen, San Diego, CA, USA; TLR-2 and TLR-4 eBioscience, San Diego, CA, USA) and FoxP3 assay (eBioscience, San Diego, CA, USA) were performed with a BD FACS Aria (BD Biosciences Pharmingen, San Diego, CA, USA)[51]. Briefly, from whole blood, PBMCs were separated with gradient centrifugation using Ficoll-Paque (GE Healthcare Life Sciences, Pittsburgh, PA, USA). The isolated PBMCs were washed twice with Phosphate Buffered Saline pH 7.4 (PBS, Central Pharmacy of Semmelweis University, Budapest, Hungary) and were stained with the appropriate fluorescent antibodies according to the manufacturers' instructions. For intracellular staining, cells were incubated first with Fixation/Permeabilization Buffer (eBioscience, San Diego, CA, USA), then washed twice with Permeabilization Buffer (eBioscience, San Diego, CA, USA) and stained by FoxP3 and isotype control. At the end of staining, cells were washed twice with PBS and with Permeabilization Buffer for the detection of cell surface markers and FoxP3, respectively. Samples were resuspended in PBS and were measured within 1 h recording at least 50 000 events in the lymphocyte gate.

Our data did not follow normal distribution, therefore non-parametric statistical tests and median and interquartile ranges were used. Mann-Whitney and Friedman tests with Dunn's post hoc comparison and Spearman's correlation were used for statistical analysis, the level of significance was 5% ($P < 0.05$). All data are expressed as median (interquartile range). Statistical analysis was performed with Statistica 8 (Statsoft, Tulsa, OK, USA).

RESULTS

Major clinical characteristics and laboratory data are summarized in Table 1. The investigated cell prevalence values and cell ratios of the adaptive and innate immune systems are summarized in Tables 2 and 3, respectively. We also highlighted the most important alterations in Figures 1 and 2.

First, we compared the immune phenotype in therapy-naïve CD patients with that of healthy controls. In CD children, the prevalence of activated T cells (i.e. $CD4^+CD25^+$ cells) increased. At the same time, the prevalence of T cells with Th1 commitment (i.e. $CD4^+CXCR3^+$ cells) decreased resulting in a skewness of Th1/Th2 to Th2. The prevalence of memory (i.e. $CD4^+CD45RO^+$) cells increased and, therefore, a shift in the naïve/memory ratio toward memory cells was observed. The prevalence of regulatory T (i.e. $CD4^+CD25^{hi}FoxP3^+$) cells was comparable between the two groups.

Striking differences in cell prevalence values of innate immunity were obtained between therapy-naïve CD and healthy children. The occurrence of NK and NKT cells (marked as $CD3^-CD161^+$ and $CD3^+6b11^+$, respectively) was lower in CD children. Interestingly, the prevalence of the APCs investigated differed largely between CD and healthy children. DCs (i.e. those with $Lin1^-HLADR^+$ expression) were more prevalent and, within DC cells, the myeloid DCs (mDCs, i.e. $CD11c^+$ cells) were more prevalent, while plasmocytoid DCs (pDCs, i.e. $CD123^+$ cells) were less frequent in CD than in healthy children. This leads to skewness of mDCs in the mDC/pDC ratio. The prevalence of peripheral monocytes (i.e. $CD14^+$ cells) also increased in therapy-naïve CD patients. In addition, the prevalence of DC cells and monocytes expressing TLR-2 and TLR-4 receptors was also increased in CD. Of note,

Table 2 Prevalence and ratios of cellular members of adaptive immunity

Cell prevalence in parent population	Control	Therapy-naïve (before conventional therapy)	First remission (with conventional therapy)	Relapse (before IFX therapy)	IFX therapy (before 2nd infusion)	IFX therapy (before 3rd infusion)
$CD4^+$ in PBMC	35.16 (24.81-47.79)	36.52 (18.61-44.06)	37.42 (22.27-44.26)	39.12 (24.15-51.18)	39.77 (27.71-50.30)	35.65 (24.31-48.81)
Activated in $CD4^+$	5.92 (2.39-6.51)	10.61 (3.93-19.04)[a]	5.03 (3.37-7.93)[g]	7.84 (5.30-11.67)[a]	7.24 (5.67-12.25)[a]	9.98 (5.45-16.19)[b]
Naïve in $CD4^+$	64.57 (59.86-73.03)	63.36 (41.19-74.86)	61.31 (39.09-73.05)	66.31 (60.44-71.79)	64.47 (53.90-77.87)	58.11 (53.51-64.96)
Effector in $CD4^+$	21.91 (13.94-33.96)	31.29 (22.80-55.78)[a]	33.97 (28.54-39.44)[a]	29.47 (26.54-36.19)[a]	35.23 (27.74-40.36)[a]	37.62 (35.74-45.24)[b,i]
Naïve/effector ratio	2.73 (1.60-4.97)	1.57 (1.02-2.54)[a]	1.43 (1.14-2.21)[a]	2.34 (1.66-2.68)	1.79 (1.47-2.36)	1.52 (1.19-1.74)[a,e]
Th1 in $CD4^+$	16.19 (9.91-25.26)	6.49 (4.50-7.67)[d]	12.89 (5.12-19.03)[c]	10.9 (4.03-14.38)[a]	12.73 (8.12-15.81)	18.87 (12.51-38.11)[e]
Th2 in $CD4^+$	4.59 (2.78-5.51)	4.7 (1.98-6.03)	5.06 (1.42-8.48)	3.97 (2.27-7.19)	4.61 (2.55-5.65)	4.46 (2.11-8.16)
Th1/Th2 ratio	3.98 (3.06-5.12)	1.60 (0.50-2.11)[d]	1.95 (0.43-3.62)[b]	2.68 (0.85-5.07)	2.68 (1.42-6.14)	3.25 (1.37-4.80)[e]
Treg in $CD4^+$	1.25 (1.10-2.37)	1.36 (1.09-2.48)	1.41 (1.07-3.50)	1.31 (1.16-2.63)	1.33 (1.07-2.99)	1.96 (1.47-3.77)[b,e]

[a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.01$ *vs* control; [c]$P < 0.05$, [g]$P < 0.01$ *vs* therapy-naïve; [e]$P < 0.05$, [i]$P < 0.01$ *vs* relapse. Data are expressed as median (interquartile range). IFX: Infliximab; PBMC: Peripheral blood mononuclear cell; Activated ($CD25^+$); Naïve ($CD45RA^+$); Effector ($CD45RO^+$); Th1: T helper 1 committed, $CXCR3^+$; Th2: T helper 2 committed, $CCR4^+$; Treg: Regulatory T lymphocytes, $CD25^{hi}FoxP3^+$.

Table 3 Prevalence and ratios of cellular members of innate immunity

Cell prevalence in parent population	Control	Therapy-naïve (before conventional therapy)	First remission (with conventional therapy)	Relapse (before IFX therapy)	IFX therapy (before 2nd infusion)	IFX therapy (before 3rd infusion)
NKT in PBMC	1.39 (0.81-2.42)	0.7 (0.11-1.33)[a]	0.74 (0.37-1.34)	0.72 (0.45-1.23)	0.73 (0.37-1.20)	0.83 (0.31-2.05)
NK in PBMC	3.17 (1.71-4.76)	1.73 (0.72-3.49)[a]	1.98 (1.65-2.97)	1.95 (0.72-4.81)	2.14 (0.66-4.78)	2.45 (1.26-4.85)
DC in PBMC	0.61 (0.10-2.15)	1.05 (0.54-3.32)[a]	1.16 (0.58-2.98)[a]	1.45 (1.09-3.46)[a]	0.86 (0.30-2.80)	0.82 (0.52-2.31)
mDC in DC	46.04 (37.14-52.30)	61.66 (45.37-72.74)[b]	45.19 (37.83-56.68)[c]	69.01 (40.11-74.79)[a,e]	60.01 (48.03-68.50)[a]	57.39 (37.19-64.14)[a,g]
pDC in DC	27.38 (20.65-33.94)	19.26 (15.08-24.58)[a]	21.61 (14.76-32.61)[a]	18.33 (16.59-26.42)[a]	19.03 (17.26-32.38)	27.39 (19.68-36.70)[g]
mDC/pDC ratio	1.85 (0.44-1.46)	3.05 (2.32-6.11)[d]	2.35 (1.80-9.10)[b,c]	3.5 (1.74-7.79)[d]	3.04 (2.03-4.65)[d]	2.20 (1.66-5.54)[b,g]
TLR-2 in DC	8.8 (4.14-17.35)	55.08 (37.27-57.94)[d]	17.32 (6.32-32.54)[c]	38.7 (19.31-54.59)[b,e]	25.89 (5.69-60.43)	16.70 (2.29-42.61)[g]
TLR-4 in DC	2.24 (0.90-2.78)	14.36 (6.26-19.20)[b]	2.73 (1.35-7.21)[f]	10.11 (2.29-19.55)[a,e]	5.31 (2.81-13.42)	3.32 (0.10-6.05)[g]
Monocyte in PBMC	2.01 (1.38-3.82)	8.57 (3.82-16.72)[b]	5.96 (2.49-21.22)[a,c]	7.3 (2.65-15.44)[a]	5.58 (2.78-17.52)[a]	5.31 (3.54-6.94)[a]
TLR-2 in monocyte	16.44 (10.31-19.69)	29.65 (17.83-39.77)[a]	20.92 (7.87-29.15)[c]	20.63 (7.05-29.01)	19.89 (13.13-29.32)	18.52 (10.29-28.96)
TLR-4 in monocyte	7.17 (0.45-14.73)	14.59 (3.01-35.23)[a]	4.43 (1.82-8.31)[c]	10.39 (2.10-26.54)	8.26 (2.71-17.56)	6.30 (2.48-18.94)

[a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.001$ *vs* control; [c]$P < 0.05$, [f]$P < 0.01$ *vs* therapy-naïve; [e]$P < 0.05$ *vs* first remission; [g]$P < 0.05$ *vs* relapse. Data are expressed as median (interquartile range). IFX: Infliximab; PBMC: Peripheral blood mononuclear cell; NK: Natural killer, $CD3^-CD161^+$; NKT: Natural killer T, $CD3^+6b11^+$; DC: Dendritic cell, Lin1-HLA-DR^+; mDC: Myeloid dendritic cell, $CD11c^+$; pDC: Plasmocytoid dendritic cell, $CD123^+$; Monocyte ($CD14^+$); TLR: Toll-like receptor.

4 of the 14 therapy-naïve CD children did not respond to conventional therapy. Their immune phenotype at the therapy-naïve phase did not differ from those children who responded to conventional therapy (data not shown).

In the second phase of our study, we prospectively tested the alteration in cell prevalence values during therapy. At the time of first remission with conventional therapy, the Th1/Th2 ratio shifted to Th1 and normalized along with activated T cell prevalence. Memory T cells remained elevated, while all the other cell types of adaptive immunity were comparable to that measured before therapy. For innate immune cells, NK and NK-T remained lower than normal and total DC prevalence remained higher than the control. However, mDC and pDC ratios, total monocyte prevalence and cells expressing TLR-2/TLR-4 receptor values (including monocytes and DCs) were normal.

In children who relapsed with conventional therapy, immune phenotype again became comparable to that in therapy-naïve CD. Therefore, we measured lower Th1, increased activated T, higher DC and higher macrophage prevalence as well as higher TLR-2 and TLR-4 expression in comparison to controls. In addition, the prevalence of mDCs, simultaneously with TLR-2 and TLR-4 expressing DCs was higher in relapsed than in remitted CD. During IFX therapy, immune cell prevalence was measured at two time points (i.e. 2 and 6 wk after the initiation of therapy). Th1, activated T and Treg prevalence increased significantly by week 6 of therapy. Total DC, mDC, pDC, total monocyte, along with TLR-2 and TLR-4 expressing DC and macrophage prevalence were normal at this time. Of note, although no significant alteration was observed at week 2, some tendencies were already present (Figures 1 and 2).

DISCUSSION

In our study we investigated the major components of adaptive and innate immunity in a simultaneous manner in CD children. While CD4 numbers in therapy-naïve CD children were normal as in early studies with adult patients[52,53], we noticed a shift to the Th2 direction in Th1/Th2 committed T lymphocytes. This finding is in line with other reports on blood[29,30,32] or biopsy specimens of therapy-naïve CD children[31]. Similar to adults, we also found a higher than normal prevalence of activated $CD4^+$ cells and effector memory cells and a decrease in effector cell/naïve CD4 cell ratios[12-17]. We tested the idea that this was

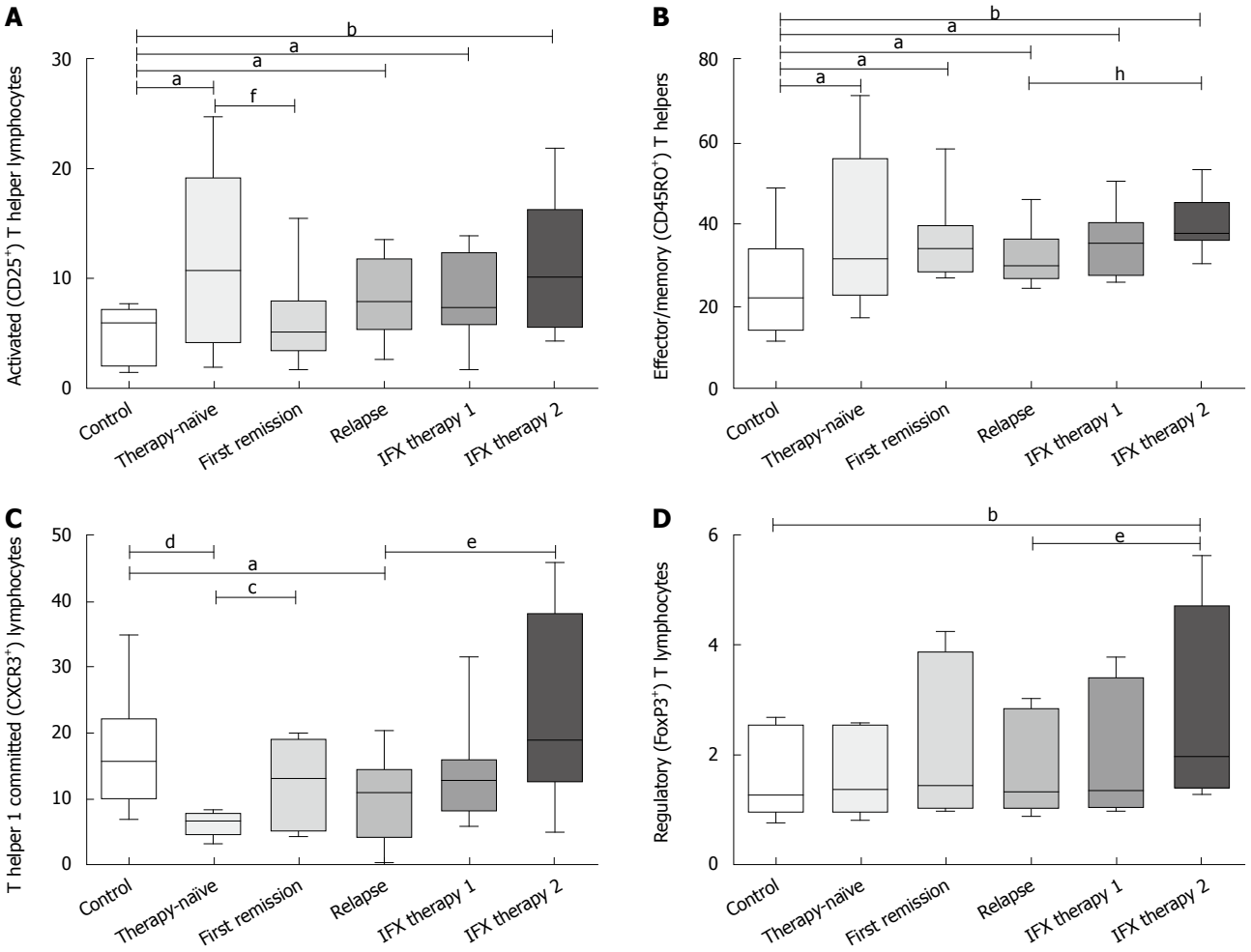

Figure 1 Prevalence of cellular members of adaptive immunity. The prevalence of activated (i.e. $CD4^+CD25^+$) (A), effector or memory (i.e. $CD4^+CXCR3^+$) (B), Th1 committed (i.e. $CD4^+CXCR3^+$) (C) and regulatory T (i.e. $CD4^+CD25hiFoxP3^+$) cells (D). $^aP < 0.05$, $^bP < 0.01$, $^dP < 0.001$ *vs* control; $^cP < 0.05$, $^fP < 0.01$ *vs* therapy-naïve; $^eP < 0.05$, $^hP < 0.01$ *vs* relapse.

due to low Treg numbers, but our data showing a normal prevalence of FoxP3 expressing CD4 cells do not support this notion. This finding is in contrast with that suggesting a diminution of Treg cells in untreated CD adults. However, in an earlier study Tregs were identified according to $CD4^+CD25^{high}$ positivity[8] currently not regarded as a sensitive marker for this cell type.

Our study provides novel information on the possible contribution of the innate immune system to a Th2 shift in therapy-naïve CD children. While some authors suggested that altered NK and NKT function may be a component in adult CD[17,26-28], our data are the first to show lower than normal NK and NKT prevalence in therapy-naïve CD children. In addition, we also observed a marked increase in monocyte and DC prevalence with an increase in the mDC/pDC ratio. These cell populations are major triggers of immune response and may be linked with the increase in memory T cell prevalence. As recent studies emphasized, mDC and pDC have distinct regulatory properties as mDC may shift the immune response not only toward Th1, but also in the Th2 direction[54], while pDC can induce Tregs[55]. Therefore, an increase in the mDC/pDC ratio in our patients may contribute to a lower Th1/Th2 ratio. Furthermore, we also measured an increased prevalence of TLR-2 and TLR-4 expressing monocytes and DCs that may also play a role in the activation of immune cells. This finding is in accordance with our previous observation of high TLR-2 and TLR-4 expression in the colonic mucosa of therapy-naïve CD children[34].

We tested prospectively the link between immune phenotype and disease activity index in our patients. The majority of immune system alterations in therapy-naïve CD are normalized with the normalization of PCDAI. While Th1 prevalence significantly increased compared to the therapy-naïve state and almost normalized during therapy, Th1/Th2 was still in the normal range at first remission suggesting a difference in CD immune phenotype between adults and children[4-7].

In remitted patients, NK and NKT prevalence increased and the difference between therapy-naïve CD and healthy controls disappeared. This finding does not support previous reports on decreased NK and NKT numbers in treated CD adults[17,26-28]. We also observed that the mDC/pDC ratio, prevalence of monocytes and that of TLR-2 and TLR-4 expressing DCs and monocytes were also normalized. This may suggest that normalization of immune phe-

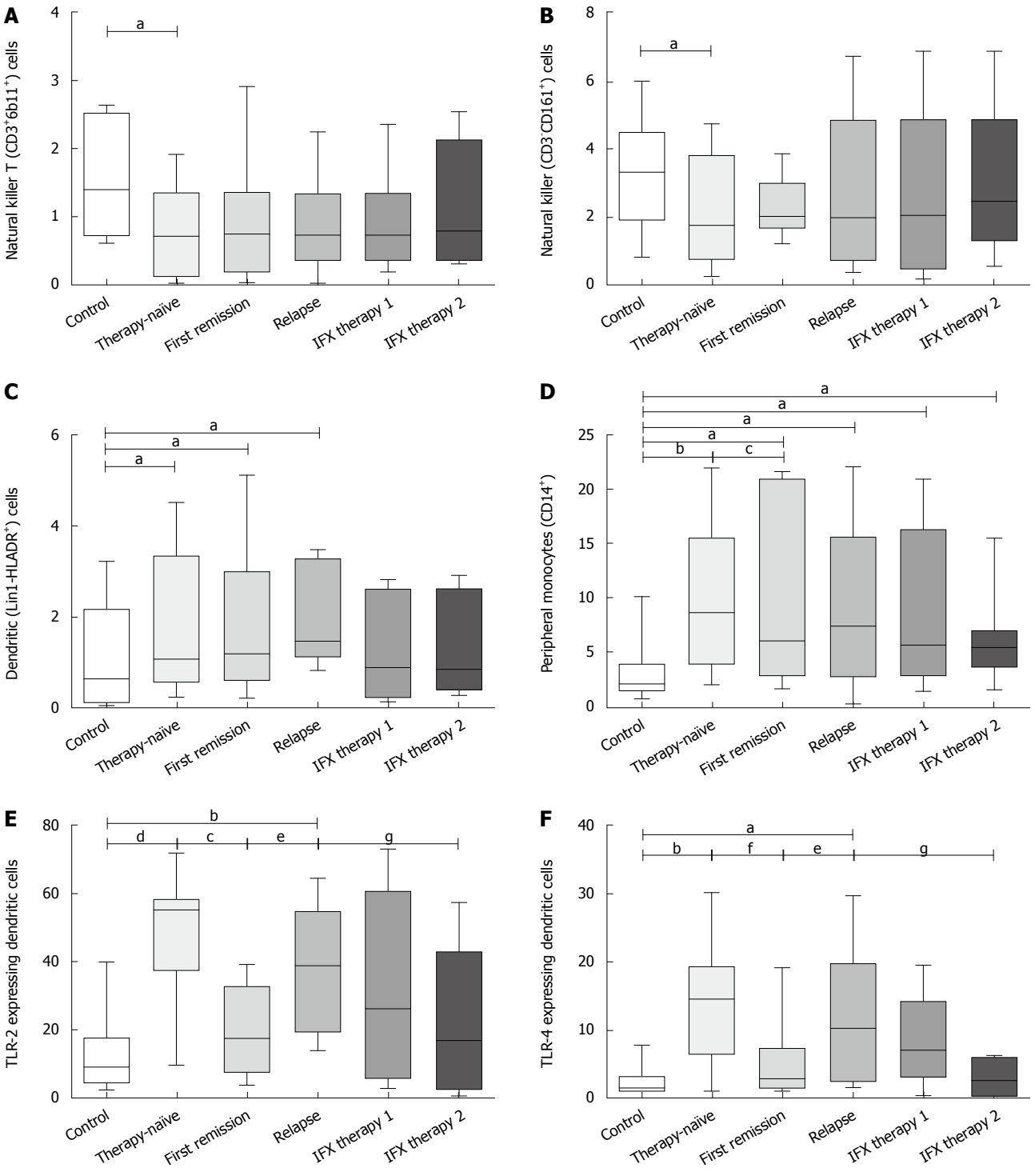

Figure 2 Prevalence of cellular members of innate immunity. The prevalence of natural killer T (i.e. $CD3^+6b11^+$) (A), natural killer (i.e. $CD3^-CD161^+$) (B), dendritic cell (i.e. $Lin1\text{-}HLA\text{-}DR^+$) (C), peripheral monocyte (i.e. $CD14^+$) (D), Toll-like receptor 2 expressing dendritic cell (E) and Toll-like receptor 4 expressing dendritic cell (F). $^aP < 0.05$, $^bP < 0.01$, $^dP < 0.001$ *vs* control; $^cP < 0.05$, $^fP < 0.01$ *vs* therapy-naïve; $^eP < 0.05$ *vs* first remission; $^gP < 0.05$ *vs* relapse.

notype is linked to an improvement in PCDAI. This may be a specific feature in childhood CD as a number of studies reported a higher than normal prevalence of activated and effector T lymphocytes even in treated CD adults[12-17]. Tregs probably do not play a role in this normalization as their prevalence was not altered in remission.

We performed another prospective study in 12 CD children who relapsed with conventional therapy and were treated with IFX. In these CD children, the immune phenotype was similar to that observed in therapy-naïve CD children (with the only exception of normal prevalence of NK and NKT cells). During IFX therapy, however, marked changes occurred in the 6th wk of IFX treatment and the prevalence of Th1 cells and the APCs investigated were normalized. Interestingly, the prevalence of activated T cells, memory cells and Treg cells were elevated further.

Recently, increased numbers of Th1 cells and high blood levels of Th1-type cytokines were found in adult patients with rheumatoid arthritis (RA) after IFX treatment[39,40]. Others also found an increase in effector and activated T cells with IFX[38,39]. While the explanation for this is still unclear, an attractive hypothesis may be that IFX inhibits the homing of Th1 and activated T cells to the inflammation site and transiently increases their peripheral occurrence[38,40].

Theoretically, this immune phenotype may refer to an increased risk for infections. However, our patients did not exhibit major clinical signs and symptoms of infection during IFX therapy. Interestingly, simultaneously with these changes, IFX therapy also increased the prevalence of peripheral Treg cells. This phenomenon - which may be due to a resistance of Tregs to IFX-induced apoptosis - was also demonstrated previously in the peripheral blood of adult CD patients[8], and in colonic samples from CD children[37].

In our patients, the prevalence of monocytes, mDCs, mDC/pDC ratio and TLR-2 and TLR-4 expressing DCs normalized during IFX therapy indicating the possible impact of biological therapy on innate immunity. This is in line with the observation of others investigating RA and CD patients[41,43-45].

Our study has three major limitations. First, although we did correct for multiplicity when performing pairwise comparisons, the study was not powered for the multitude of statistical tests we performed, thus some significances could occur by chance alone. Second, peripheral cell prevalence values do not necessarily reflect the intestinal phenotype. Third, our results may have been affected by ageing of the patients during the follow-up period. The short duration of our prospective study (i.e. about 10 mo until the first remission or 6 wk from the beginning of IFX therapy), however, makes this bias less likely.

CD exhibits several abnormalities in adaptive immunity (such as a decrease in Th1 cell and an increase in memory and activated T cell prevalence) and innate immunity (such as an increase in DC, monocyte and TLR-2 and TLR-4 exhibiting APC prevalence). The majority of the observed alterations of the innate immune system are normalized with the improvement of clinical signs and symptoms of CD, irrespective of whether this is obtained by conventional therapy or add-on IFX therapy. This finding suggests a link between immune phenotype and disease activity in childhood CD.

If these results are reinforced by other groups, the observations may raise the possibility that immune phenotype is a potential biomarker for clinical response in CD children.

COMMENTS

Background

About 10%-15% of patients with Crohn's disease (CD) are diagnosed before 18 years of age. Pediatric CD is a unique subtype of CD due to different location, altered responsiveness to therapy and different susceptibility factors compared with those in adult CD.

Research frontiers

Several studies indicate both the malfunction of adaptive and innate immunity in adulthood CD. Fewer data are available for CD children. The alteration of immune phenotype with treatment is also unclear in this population.

Innovations and breakthroughs

In this prospective study, the authors demonstrated marked alterations in both adaptive and innate immunity in childhood CD. These abnormalities were resolved in infants responding to conventional therapy but not in non-responding children. Immune phenotype depends on disease activity.

Applications

These observations support the involvement of members of the adaptive and innate immune systems in childhood CD. They also identify immune phenotype as a possible biomarker for the follow-up of therapeutic success.

Peer review

In this study, the authors prospectively investigated the major components of adaptive and innate immunity in CD children. The authors showed several abnormalities in adaptive and innate immunity in CD children. They also showed that the majority of observed alterations were normalized in remission stage and suggest a link between immune phenotype and disease activity in childhood CD. Although the number of CD patients enrolled to this study was small, this prospective study demonstrated clinically interesting results in CD children.

REFERENCES

1 **Dubinsky M**. Special issues in pediatric inflammatory bowel disease. *World J Gastroenterol* 2008; **14**: 413-420
2 **Nieuwenhuis EE**, Escher JC. Early onset IBD: what's the difference? *Dig Liver Dis* 2008; **40**: 12-15
3 **Shaoul R**, Karban A, Reif S, Weiss B, Shamir R, Tamir A, Davidovich O, Halevi J, Silver EL, Levine A. Disease behavior in children with Crohn's disease: the effect of disease duration, ethnicity, genotype, and phenotype. *Dig Dis Sci* 2009; **54**: 142-150
4 **Zenewicz LA**, Antov A, Flavell RA. CD4 T-cell differentiation and inflammatory bowel disease. *Trends Mol Med* 2009; **15**: 199-207
5 **Himmel ME**, Hardenberg G, Piccirillo CA, Steiner TS, Levings MK. The role of T-regulatory cells and Toll-like receptors in the pathogenesis of human inflammatory bowel disease. *Immunology* 2008; **125**: 145-153
6 **van Lierop PP**, Samsom JN, Escher JC, Nieuwenhuis EE. Role of the innate immune system in the pathogenesis of inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2009; **48**: 142-151
7 **Sartor RB**. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 390-407
8 **Chamouard P**, Monneaux F, Richert Z, Voegeli AC, Lavaux T, Gaub MP, Baumann R, Oudet P, Muller S. Diminution of Circulating CD4+CD25 high T cells in naïve Crohn's disease. *Dig Dis Sci* 2009; **54**: 2084-2093
9 **Maul J**, Loddenkemper C, Mundt P, Berg E, Giese T, Stallmach A, Zeitz M, Duchmann R. Peripheral and intestinal regulatory CD4+ CD25(high) T cells in inflammatory bowel disease. *Gastroenterology* 2005; **128**: 1868-1878
10 **Saruta M**, Yu QT, Fleshner PR, Mantel PY, Schmidt-Weber CB, Banham AH, Papadakis KA. Characterization of FOXP3+CD4+ regulatory T cells in Crohn's disease. *Clin Immunol* 2007; **125**: 281-290
11 **Makita S**, Kanai T, Oshima S, Uraushihara K, Totsuka T, Sawada T, Nakamura T, Koganei K, Fukushima T, Watanabe M. CD4+CD25bright T cells in human intestinal lamina propria as regulatory cells. *J Immunol* 2004; **173**: 3119-3130
12 **Roman LI**, Manzano L, De La Hera A, Abreu L, Rossi I, Alvarez-Mon M. Expanded CD4+CD45RO+ phenotype and defective proliferative response in T lymphocytes from patients with Crohn's disease. *Gastroenterology* 1996; **110**: 1008-1019
13 **Alkim C**, Balci M, Alkim H, Dağli U, Parlak E, Tezel A, Ulker

A. The importance of peripheral immune cells in inflammatory bowel disease. *Turk J Gastroenterol* 2007; **18**: 82-88
14 **García de Tena J**, Manzano L, Leal JC, San Antonio E, Sualdea V, Alvarez-Mon M. Active Crohn's disease patients show a distinctive expansion of circulating memory CD4+CD45RO+CD28null T cells. *J Clin Immunol* 2004; **24**: 185-196
15 **Rose M**, Hildebrandt M, Fliege H, Seibold S, Mönnikes H, Klapp BF. T-cell immune parameters and depression in patients with Crohn's disease. *J Clin Gastroenterol* 2002; **34**: 40-48
16 **Liu ZX**, Hiwatashi N, Noguchi M, Toyota T. Increased expression of costimulatory molecules on peripheral blood monocytes in patients with Crohn's disease. *Scand J Gastroenterol* 1997; **32**: 1241-1246
17 **Senju M**, Hulstaert F, Lowder J, Jewell DP. Flow cytometric analysis of peripheral blood lymphocytes in ulcerative colitis and Crohn's disease. *Gut* 1991; **32**: 779-783
18 **Zenewicz LA**, Antov A, Flavell RA. CD4 T-cell differentiation and inflammatory bowel disease. *Trends Mol Med* 2009; **15**: 199-207
19 **Baumgart DC**, Metzke D, Schmitz J, Scheffold A, Sturm A, Wiedenmann B, Dignass AU. Patients with active inflammatory bowel disease lack immature peripheral blood plasmacytoid and myeloid dendritic cells. *Gut* 2005; **54**: 228-236
20 **Baumgart DC**, Thomas S, Przesdzing I, Metzke D, Bielecki C, Lehmann SM, Lehnardt S, Dörffel Y, Sturm A, Scheffold A, Schmitz J, Radbruch A. Exaggerated inflammatory response of primary human myeloid dendritic cells to lipopolysaccharide in patients with inflammatory bowel disease. *Clin Exp Immunol* 2009; **157**: 423-436
21 **Hart AL**, Al-Hassi HO, Rigby RJ, Bell SJ, Emmanuel AV, Knight SC, Kamm MA, Stagg AJ. Characteristics of intestinal dendritic cells in inflammatory bowel diseases. *Gastroenterology* 2005; **129**: 50-65
22 **Frolova L**, Drastich P, Rossmann P, Klimesova K, Tlaskalova-Hogenova H. Expression of Toll-like receptor 2 (TLR2), TLR4, and CD14 in biopsy samples of patients with inflammatory bowel diseases: upregulated expression of TLR2 in terminal ileum of patients with ulcerative colitis. *J Histochem Cytochem* 2008; **56**: 267-274
23 **Kamada N**, Hisamatsu T, Honda H, Kobayashi T, Chinen H, Kitazume MT, Takayama T, Okamoto S, Koganei K, Sugita A, Kanai T, Hibi T. Human CD14+ macrophages in intestinal lamina propria exhibit potent antigen-presenting ability. *J Immunol* 2009; **183**: 1724-1731
24 **Cantó E**, Ricart E, Monfort D, González-Juan D, Balanzó J, Rodríguez-Sánchez JL, Vidal S. TNF alpha production to TLR2 ligands in active IBD patients. *Clin Immunol* 2006; **119**: 156-165
25 **Grimm MC**, Pavli P, Van de Pol E, Doe WF. Evidence for a CD14+ population of monocytes in inflammatory bowel disease mucosa--implications for pathogenesis. *Clin Exp Immunol* 1995; **100**: 291-297
26 **van Ierssel GJ**, van der Sluys Veer A, Verspaget HW, Griffioen G, van Hogezand RA, Lamers CB. Contribution of plasma cortisol to corticosteroid-suppressed peripheral blood natural killer cell activity in Crohn's disease. *Immunopharmacology* 1995; **29**: 11-17
27 **Grose RH**, Thompson FM, Baxter AG, Pellicci DG, Cummins AG. Deficiency of invariant NK T cells in Crohn's disease and ulcerative colitis. *Dig Dis Sci* 2007; **52**: 1415-1422
28 **Kontiainen S**, Scheinin T, Halme L. Number of activated T-helper cells and NK cells in peripheral blood is decreased in severe Crohn's disease. *APMIS* 1996; **104**: 355-361
29 **Mack DR**, Beedle S, Warren J, Davis J, Gross T. Peripheral blood intracellular cytokine analysis in children newly diagnosed with inflammatory bowel disease. *Pediatr Res* 2002; **51**: 328-332
30 **Holland N**, Dong J, Garnett E, Shaikh N, Huen K, Harmatz P, Olive A, Winter HS, Gold BD, Cohen SA, Baldassano RN, Kirschner BS, Heyman MB. Reduced intracellular T-helper 1 interferon-gamma in blood of newly diagnosed children with Crohn's disease and age-related changes in Th1/Th2 cytokine profiles. *Pediatr Res* 2008; **63**: 257-262
31 **Desreumaux P**, Brandt E, Gambiez L, Emilie D, Geboes K, Klein O, Ectors N, Cortot A, Capron M, Colombel JF. Distinct cytokine patterns in early and chronic ileal lesions of Crohn's disease. *Gastroenterology* 1997; **113**: 118-126
32 **Jo Y**, Matsumoto T, Yada S, Fujisawa K, Esaki M, Onai N, Matsushima K, Iida M. CCR4 is an up-regulated chemokine receptor of peripheral blood memory CD4+ T cells in Crohn's disease. *Clin Exp Immunol* 2003; **132**: 332-338
33 **Perminow G**, Reikvam DH, Lyckander LG, Brandtzaeg P, Vatn MH, Carlsen HS. Increased number and activation of colonic macrophages in pediatric patients with untreated Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1368-1378
34 **Szebeni B**, Veres G, Dezsõfi A, Rusai K, Vannay A, Mraz M, Majorova E, Arató A. Increased expression of Toll-like receptor (TLR) 2 and TLR4 in the colonic mucosa of children with inflammatory bowel disease. *Clin Exp Immunol* 2008; **151**: 34-41
35 **Diefenbach KA**, Breuer CK. Pediatric inflammatory bowel disease. *World J Gastroenterol* 2006; **12**: 3204-3212
36 **Veres G**, Baldassano RN, Mamula P. Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs* 2007; **67**: 1703-1723
37 **Ricciardelli I**, Lindley KJ, Londei M, Quaratino S. Anti tumour necrosis-alpha therapy increases the number of FOXP3 regulatory T cells in children affected by Crohn's disease. *Immunology* 2008; **125**: 178-183
38 **Ferkolj I**, Ihan A, Markovic S, Veceric Z, Pohar M. Infliximab reduces the number of activated mucosal lymphocytes in patients with Crohn's disease. *J Gastrointestin Liver Dis* 2006; **15**: 231-235
39 **Aeberli D**, Seitz M, Jüni P, Villiger PM. Increase of peripheral CXCR3 positive T lymphocytes upon treatment of RA patients with TNF-alpha inhibitors. *Rheumatology* (Oxford) 2005; **44**: 172-175
40 **Maurice MM**, van der Graaff WL, Leow A, Breedveld FC, van Lier RA, Verweij CL. Treatment with monoclonal anti-tumor necrosis factor alpha antibody results in an accumulation of Th1 CD4+ T cells in the peripheral blood of patients with rheumatoid arthritis. *Arthritis Rheum* 1999; **42**: 2166-2173
41 **Richez C**, Schaeverbeke T, Dumoulin C, Dehais J, Moreau JF, Blanco P. Myeloid dendritic cells correlate with clinical response whereas plasmacytoid dendritic cells impact autoantibody development in rheumatoid arthritis patients treated with infliximab. *Arthritis Res Ther* 2009; **11**: R100
42 **Balanescu A**, Radu E, Nat R, Regalia T, Bojinca V, Ionescu R, Balanescu S, Savu C, Predeteanu D. Early and late effect of infliximab on circulating dendritic cells phenotype in rheumatoid arthritis patients. *Int J Clin Pharmacol Res* 2005; **25**: 9-18
43 **Lügering A**, Schmidt M, Lügering N, Pauels HG, Domschke W, Kucharzik T. Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase-dependent pathway. *Gastroenterology* 2001; **121**: 1145-1157
44 **Baert FJ**, D'Haens GR, Peeters M, Hiele MI, Schaible TF, Shealy D, Geboes K, Rutgeerts PJ. Tumor necrosis factor alpha antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology* 1999; **116**: 22-28
45 **De Rycke L**, Vandooren B, Kruithof E, De Keyser F, Veys EM, Baeten D. Tumor necrosis factor alpha blockade treatment down-modulates the increased systemic and local expression of Toll-like receptor 2 and Toll-like receptor 4 in spondylarthropathy. *Arthritis Rheum* 2005; **52**: 2146-2158
46 Inflammatory bowel disease in children and adolescents: recommendations for diagnosis--the Porto criteria. *J Pediatr Gastroenterol Nutr* 2005; **41**: 1-7
47 **Hyams JS**, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, Griffiths AM, Katz AJ, Grand RJ, Boyle JT.

Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991; **12**: 439-447
48 **Satsangi J**, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; **55**: 749-753
49 **Mamula P**, Markowitz JE, Baldassano RN. Inflammatory bowel disease in early childhood and adolescence: special considerations. *Gastroenterol Clin North Am* 2003; **32**: 967-995, viii
50 **Diefenbach KA**, Breuer CK. Pediatric inflammatory bowel disease. *World J Gastroenterol* 2006; **12**: 3204-3212
51 **Svec P**, Vásárhelyi B, Pászthy B, Körner A, Kovács L, Tulassay T, Treszl A. Do regulatory T cells contribute to Th1 skewness in obesity? *Exp Clin Endocrinol Diabetes* 2007; **115**: 439-443
52 **Selby WS**, Jewell DP. T lymphocyte subsets in inflammatory bowel disease: peripheral blood. *Gut* 1983; **24**: 99-105
53 **Yuan SZ**, Hanauer SB, Kluskens LF, Kraft SC. Circulating lymphocyte subpopulations in Crohn's disease. *Gastroenterology* 1983; **85**: 1313-1318
54 **Kool M**, Lambrecht BN. Dendritic cells in asthma and COPD: opportunities for drug development. *Curr Opin Immunol* 2007; **19**: 701-710
55 **de Heer HJ**, Hammad H, Kool M, Lambrecht BN. Dendritic cell subsets and immune regulation in the lung. *Semin Immunol* 2005; **17**: 295-303

S- Editor Tian L **L- Editor** Webster JR **E- Editor** Ma WH