The use of thiopurine monotherapy or in combination with anti-engineered drugs, targeting specific steps of the inflammatory advent of a new class of drugs, the biologics, i.e. genetically disease (IBD) has been dramatically revolutionized by the biologics, mechanism of action.

In the last two decades management of inflammatory bowel disease has been dramatically revolutionized by the advent of a new class of drugs, the biologics, i.e. genetically engineered drugs, targeting specific steps of the inflammatory cascade underlying IBD. The first and more extensively used biologics have been those neutralizing TNFa, a cytokine delivered in the earliest phases of the inflammatory process and playing a pivotal role.

The anti-TNFa agents have extensively been used both in adults and children with IBD; however, IBD children seem to respond better than adults in terms of remission and response. More recently, compared to traditional therapy biologics have been shown to promote higher rates of mucosal healing, that has been associated to prolonged remission, reduced rate of corticosteroid exposure, hospitalization and surgery. It has been also suggested that the early use of biologics can alter the natural disease course, by interrupting or slowing the progression to more complicated forms of the disease.

Despite the effectiveness of biologics, up to one/third of patients do not respond to anti-TNFa therapy and, of those with initial response, the majority can lose response or exhibit intolerance to one or more of the medications within the anti-TNFa class. Thus, new knowledge in the pathogenesis of IBD, mainly through animal model of colitis, has resulted in the implementation of new biologic agents aiming at counteracting other steps of the inflammatory process such as the IL-23 axis, the JAK-STAT signaling pathways, adhesion molecules, chemokine antagonists and cytokine blockers.

Safety of immunosuppressives and biologicals

J.S. Hyams*. Connecticut Childrens Medical Center, Hartford, United States of America

Immunosuppressive (IM) use is noted in up to 75% of children newly diagnosed with CD and 40% of those with UC; biological therapy is seen in up to 40% of those with CD and 20% of those with UC (Ped IBD Collap Grp Registry, 2014, unpublished data). Serious infection and malignancy are the two potential complications of greatest concern and may influence patient and parental acceptance of these therapies. Recent data suggest that the rate of serious infections for children treated with anti-TNFa is similar to that of patients receiving IM monotherapy, but less than for children treated with steroids or adults treated with anti-TNFa agents. The risk of lymphoma does not appear greater in children with IBD who receive anti-TNFa monotherapy in adults at least the risk of lymphoma is increased 4-fold in those exposed to thiopurine therapy. The potential additive contribution to cancer risk of combination therapy with anti-TNFa and thiopurines remains a concern; whether there is an additional risk with combined anti-TNFa and methotrexate is not known. The development of hepatosplenic T-cell lymphoma (HSTCL), a rare and usually fatal disorder, appears to be largely associated with thiopurine use, especially prolonged exposure. Combination therapy with anti-TNFa and thiopurine, especially in young males, is associated with increased risk of HSTCL. Concerns about malignancy will persist, but anti-TNFa therapy appears safe. The use of thiopurine monotherapy or in combination with anti-TNFa agents continues to engender concerns. The safety of methotrexate as an alternative IM remains to be determined.

New biologicals, mechanism of action

S. Cucchiara*, M. Aloi. Sapienza University of Rome, Rome, Italy

In the last two decades management of inflammatory bowel disease (IBD) has been dramatically revolutionized by the advent of a new class of drugs, the biologics, i.e. genetically engineered drugs, targeting specific steps of the inflammatory cascade underlying IBD. The first and more extensively used biologics have been those neutralizing TNFa, a cytokine delivered in the earliest phases of the inflammatory process and playing a pivotal role.

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Oral versus subcutaneous methotrexate (MTX) in pediatric Crohn's disease (CD): a multicenter propensity propensity score (PS) study

D. Turner1, E. Doveh2, A. Cohen3, M.L. Wilson4, D.C. Wilson3, A.B. Grossman4, J. Rosh5, Y.L. Lu6, A. Noble7, R. Baldassano4, A. Levine8, A. Lerner9, A. Bousvaros5, A. Griffiths10, 1 Shaare Zedek Medical Center, Jerusalem, Israel, 2Technion, Haifa, Israel, 3Edinburgh, Edinburgh, United Kingdom, 4CHOP, Philadelphia, United States of America, 5NJ, NJ, United States of America, 6Boston, Boston, United States of America, 7Montreal, Montreal, Canada, 8Wolfson, Holon, Israel, 9Carmel, Hafa, Israel, 10HSC, Toronto, Canada

Background: We aimed to compare effectiveness and adverse events of orally vs subcutaneously administered MTX in pediatric CD.

Methods: 226 children with established CD treated with oral or SC MTX entered a multicenter, retrospective 1-yr cohort study [62% males, mean age 13.8±2.8 yrs, 88% with previous thiopurines, disease duration 1.9 months (IQR 0.9–4)]. 38 (17%) were initially commenced on PO, 98 (43%) started SC and switched to PO and 90 (40%) were treated with SC only. Matching and ‘doubly robust’ regression weighting were based on the PS method, a powerful tool to control for confounding-by-indication bias. 11/23 pre-treatment variables were different between the groups, but none remained significant after adjustment, indicating that PS modeling balanced the treatment groups.

Results: 76 children (3%) had sustained steroid-free remission and this did not differ between the PO and SC groups [OR = 1.72 (95% CI 0.5–5.9); P = 0.52]. There were no differences in the need for treatment escalation (P = 0.24, P = 0.58 and P = 0.13), elevated liver enzymes (P = 0.59) and nausea (P = 0.85). Height velocity was lower in the PO group (P = 0.006) but in an individual matching the PO group was not inferior. According to Fleming test, time to remission was delayed in the PO group (P = 0.036), but not according to the log-rank test P = 0.23.

Conclusions: In this largest cohort to date on MTX in pediatric CD, no differences were found between PO and SC administered MTX in children with CD, suggesting that it may be reasonable to switch children in complete remission treated with SC MTX to the oral route.